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THE LEVELS OF CIRCULATING EOSINOPHILS AND THEIR RESPONSE TO ACTH IN SURGERY*

Their Use As an Index of Adrenocortical Function

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BOSTON AND PHILADELPHIA

THE levels of circulating eosinophils are intimately related to the activity of the adrenal cortex. Alarming stimuli, when applied to animals, are followed by a marked fall in the level of circulating eosinophils.[1, 2] Regarding the mechanism of this eosinopenia, it is known that stress leads to the release of adrenocorticotrophic hormone (ACTH) by the hypophysis; ACTH in turn stimulates the adrenal cortex, which releases its steroid hormones in large quantities; of these steroids, those with an oxygen atom on the 11 and 17 carbon positions (the so-called "11-17 oxysteroids") produce by a mechanism as yet unknown the fall in eosinophil levels.[3, 4]

A similar eosinopenia may be obtained by the injection of epinephrine or purified ACTH.[4, 5] Injected ACTH acts through direct stimulation of the adrenal cortex. Epinephrine injected in small doses (0.3 mg.) appears to act through stimulation of the hypothalamus or the hypophysis and secondary stimulation of the adrenal cortex.[4] A direct action on eosinophils of relatively large doses — for example, 1.5 mg. — of epinephrine has not been excluded.[4]

The measurement of the fall in circulating eosinophils four hours after the injection of ACTH or small doses of epinephrine subcutaneously forms the basis of clinical tests for adrenocortical and pituitary-adrenocortical reserves respectively.[4, 6]

The integrity of the adrenal cortex is essential for survival in a major surgical operation. It is well known, for instance, that patients with Addison's disease and adrenalectomized animals seldom survive even minor surgical procedures unless they are protected by large quantities of adrenal hormones, particularly those of the "11-oxy" type.[7-12] After surgical operation in patients with intact adrenal glands there appears to be a greatly increased functional activity of the glands reflected in an increased titer of the urinary metabolic end products of their hormones.[1, 13, 14]

In spite of the obvious importance of these glands, their role and contribution in the symptomatology and chemical changes characteristic of the postoperative malady have not been clearly delineated. In view of the marked demand placed on the adrenal cortex during and after operation, one might expect to encounter on occasion a relative or absolute deficiency as a clinical entity. In the past, it has been almost impossible to detect this syndrome with certainty. Hence adrenocortical hormone has been administered half heartedly in doses totally inadequate if insufficiency were actually present. This may explain in part the poor results generally obtained in man,[15] as compared (with few exceptions[16]) with those obtained in animals by the use of adrenocortical extracts or pure adrenal steroids.[8-11]

The estimation of the blood level of eosinophils has been utilized for a long time as a prognostic aid, although the connection with adrenocortical function was of course not suspected. Lams,[17] for instance, quoted Chantemesse and Rey (1899) as stating that, from the hematologic point of view, "les maladies évoluent en général par les stades de polynucléose, mononucléose et enfin éosinophilie." He himself found that, during the acute stage of diseases, the eosinophils disappeared almost entirely from the blood, to reappear and even increase during recovery; eosinophilia to him was an "index of convalescence."

A knowledge of the natural course of the eosinophil levels during and after surgery and of their response to ACTH should help in the assay of adrenocortical function postoperatively. Such information might provide a practical basis for estimating the need for supplementary adrenocortical extract

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therapy or crystalline 11-17 oxysteroids when the latter become available.

Methods and Materials

Measurement of the eosinophil levels was carried out by a modification of the method of Dunger.[5, 18] Bottles for the collection of blood are prepared in advance by placing in a suitable container and evaporating to dryness 0.5 cc. of the following solution:

Substance	Amount
	gm.
Potassium oxalate	0.8
Ammonium oxalate	1.2
Distilled water to 100 cc.	

Oxalate solution in the amount of 0.5 cc. will prevent the coagulation of 5 cc. of blood. The blood is obtained by venipuncture. In the absence of circulatory stasis capillary blood may be used.

Eosinophil Count

The blood is drawn into an ordinary white-cell-count pipette to the 0.5 mark, after which a special fluid is used to complete the dilution to the 11 mark. The composition of the special fluid is as follows:

Substance	Amount
	cc.
Aqueous yellowish eosin, 2 per cent	5
Acetone	5
Distilled water	90

After dilution of the blood with this fluid, the pipette is shaken at once *for thirty seconds only*; the counting chamber is filled immediately. After an interval of *three minutes*, the eosinophils are counted. These cells may be identified by their deeply staining red granules. A special Levy chamber (0.2 mm. in depth) is used, and the average of four chambers is computed. The chamber count divided by 16 and multiplied by 100 yields the number of eosinophils per cubic millimeter. The counting pipettes, once filled, cannot be allowed to stand, and the count must be performed promptly.[5, 6] Normal eosinophil counts average 180, with a range from 60 to 50 per cubic millimeter.

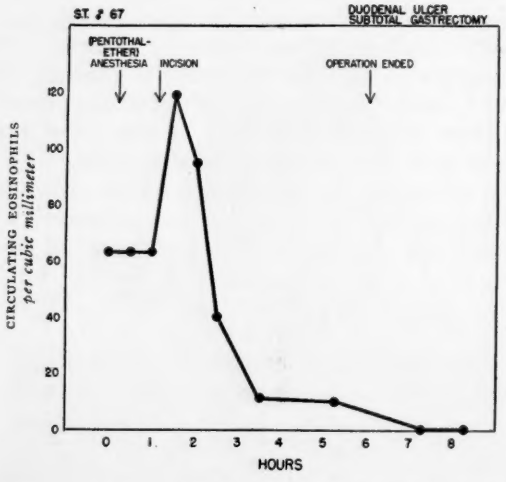

Figure 1. *Changes in Circulating Eosinophils during a Major Surgical Procedure.*

As an example, if the individual chamber count in four different chambers is 32, 37, 31 and 30 the average chamber count will be 32.5. The number of eosinophils per cubic millimeter will be 32.5 times 100 divided by 16, which equals 203 per cubic millimeter.

ACTH and Epinephrine Tests

The ACTH and epinephrine tests were carried out as follows: blood for the eosinophil count was obtained; 25 mg. of ACTH was administered intramuscularly, or 0.3 mg. of epinephrine subcutaneously. Blood for the eosinophil count was again obtained four hours later. A fall of 50 per cent or more from the initial level in the eosinophil count *four hours* after the administration of either ACTH or epinephrine was taken to indicate normal adrenocortical or pituitary-adrenocortical reserves, respectively.

The eosinophil counts and ACTH and epinephrine tests were generally done in the morning, with the patient at bed rest throughout the period of the test. Meals were arranged so that the second specimen was obtained at least three hours after the last meal. Some tests were carried out at any time during the day or night, whenever the question of the possibility of adrenal insufficiency arose. No attempt was made to measure urinary uric acid excretion.

ACTH (Armour) was provided as a sterile, lyophilized powder, 25 mg. of which was dissolved in 2 cc. of saline solution for intramuscular injection. The quantity of ACTH used refers to the equivalent of the Armour Standard La-1-A in all cases.*

Results

Eosinophil Levels during Operation

The eosinophil levels were followed every half hour throughout operation in 3 patients. Two patients were men who underwent a total gastrectomy and colectomy. One of the patients, a woman, was subjected to a subtotal thyroidectomy. In all 3 cases anesthesia was induced with Pentothal and continued with ether. All 3 patients had a similar response, one of which is illustrated in Figure 1. Regardless of the control levels, the eosinophils doubled their value within half an hour of the beginning of operation, and then fell abruptly, reaching their minimum about four to six hours after the incision had been made.

*We are indebted to Dr. John R. Mote, Armour Laboratories, Chicago 9, Illinois, for the supply of ACTH, and to the Department of Products Research, Parke-Davis and Company, for the supply of Eschatin and Adrenalin.

Eosinophil Levels Immediately after Operation

The eosinophil levels were determined five to eight hours after the beginning of a major operation (Pentothal and ether anesthesia) in 50 patients. In 29 cases, a control level had been obtained on the day before operation. The markedly reduced initial eosinophil levels (10 to 60 cells per cubic millimeter) in 8 of the cases are thought to represent the patients' reaction to stress (infection, hemorrhage or anxiety) prior to the operative procedure. In every case the postoperative value was found to be very low, and in all except 2 it was less than 20 eosinophils per cubic millimeter. In 19 cases the eosinophils disappeared entirely from the blood. *In all the cases* in which a preoperative value had been obtained, the fall was profound, varying from 86 to 100 per cent (Fig. 2).

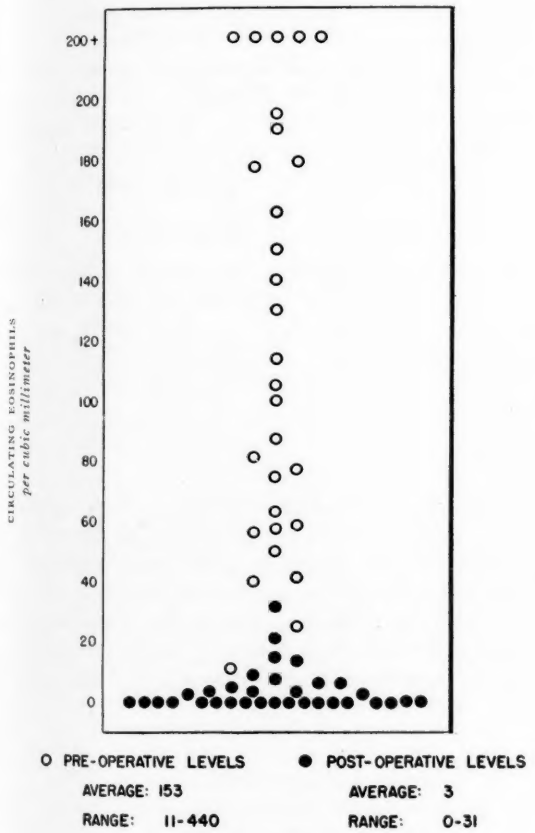

FIGURE 2. *Levels of Circulating Eosinophils before and after Major Surgical Procedures (Pentothal and Ether Anesthesia Was Employed).*

Eosinophil Levels during the Postoperative Period

In 18 patients the eosinophil level was followed during the postoperative period for a varying number of days. The results are illustrated in Figure 3. The marked postoperative eosinopenia continued usually for one or two days. Between the second and the fourth day after surgery, there was usually a sharp rise in the eosinophil levels, the preoperative values being attained or exceeded. The rise usually coincided with clinical improvement.

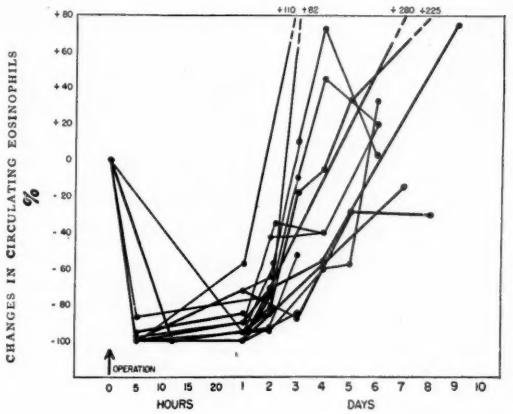

FIGURE 3. *Changes in Circulating Eosinophils after a Major Operation.*

To interpret this rise it appeared essential to measure adrenal and pituitary-adrenal reserve at this time. Accordingly, a number of patients were tested with 25 mg. of ACTH or 0.3 mg. of epinephrine, the eosinophil levels being measured before injection and four hours later. A characteristic response to ACTH (Fig. 4) was that of a sixty-three-year-old man who underwent a subtotal pancreatectomy lasting approximately seven hours. Preoperatively a fall of 65 per cent in the eosinophils followed the administration of ACTH, indicating a normal adrenocortical reserve. After operation the level of eosinophils fell from 160 per cubic millimeter to 0. On the third postoperative day,

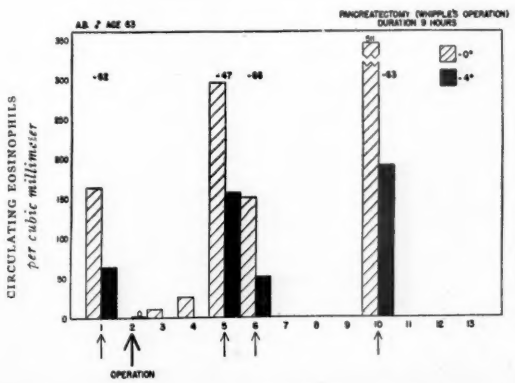

FIGURE 4. *Preoperative and Postoperative Response to ACTH. Each arrow indicates the injection of 25 mg. of ACTH.*

the eosinophils rose to 265 per cubic millimeter. A fall of 45 per cent followed the administration of 25 mg. of ACTH and suggested a nearly normal adrenocortical reserve at this time that appeared consistent with the excellent clinical condition and uneventful convalescence. Normal responses to ACTH were also obtained on the fourth and seventh postoperative days.

In Table 1 are summarized the observations on patients who showed a normal response to the administration of ACTH or epinephrine or both at or near the time of the postoperative eosinophil rise. These results suggest a return of normal adrenal and pituitary reserve at this point in postoperative convalescence. Patients with eosinophil levels below 75 per cubic millimeter and a normal response to ACTH or epinephrine suggest that despite a continued increase of adrenal steroid secretion (relative eosinopenia), *reserve* adrenocortical function had been restored to normal.

Table 1. *Response of the Rising Postoperative Eosinophil Level to ACTH or Epinephrine.*

Patient	Operation	Postoperative Day	Eosinophils before test per cu. mm.	Eosinophils after 4 hr. per cu. mm.	Change %
Epinephrine test*:					
S. T.	Gastrectomy	4	38	16	−58
R. P.	Nephrectomy	6	100	50	−50
F. K.	Thyroidectomy	3	225	97	−57
N. M.	Hysterectomy	5	319	138	−57
R. R.	Hysterectomy	3	106	19	−82
C. M.	Cholecystectomy	5	56	25	−55
W. M.	Cordotomy	2	58	28	−52
M. G.	Tonsillectomy	3	185	56	−70
ACTH test†:					
A. B.	Pancreatectomy	3	295	157	−47
T. S.	Nephrectomy	3	400	76	−81
T. T.	Colostomy	3	63	20	−68
M. C.	Laparotomy	5	161	71	−56
C. H.	Laparotomy	5	126	6	−95
N. M.	Hysterectomy	2	331	29	−91
R. R.	Hysterectomy	3	106	19	−82

*0.3 mg. subcutaneously.
†25 mg intramuscularly.

Five patients tested with epinephrine (Table 2) had subnormal responses. All however showed a normal response to ACTH on the same or the following day, suggesting adequate adrenocortical reserve in the presence of a depleted or refractory anterior pituitary gland.

Table 2. *Dissociation of the ACTH and Epinephrine Responses Postoperatively.*

Patient	Operation	Epinephrine Test* Postoperative Day	Before test eosinophils/cu. mm.	After 4 hr. eosinophils/cu. mm.	Change %
R. S.	Disk removal	3	90	56	−38
M. W.	Appendectomy	3	218	159	−27
E. G.	Appendectomy	3	62	53	−14
P. L.	Colectomy	3	95	105	+10
J. G.	Arthrotomy	3	84	123	+32

*0.3 mg. subcutaneously.
†25 mg. intramuscularly.

Effect of Preoperative Anxiety on Eosinophil Level

In most cases preoperative tension appears to play a definite but minor role in modifying the eosinophil level. The mean value in the entire group of patients studied preoperatively was 153 eosinophils per cubic millimeter as compared with 181 for normal control subjects. Occasionally, patients showed very low preoperative values, such as 10 to 60 cells per cubic millimeter. It is not possible, in certain cases, to exclude the effect of the underlying pathologic process on the initial eosinophil level, since one might expect infection, hemorrhage and so forth to induce varying degrees of eosinopenia. In patients without evidence of infection who were followed for several days before operation it is of interest to note that in almost every case there was a gradual, progressive lowering of the eosinophil count as the day of operation approached.

Effect of Anesthesia on Eosinophil Level

All patients so far discussed in this study had Pentothal-induced ether anesthesia. Four patients who underwent minor procedures such as sigmoidoscopy and radium implantation with Pentothal anesthesia had no fall in the level of eosinophils.

Ether itself did not produce eosinopenia in dogs.[19] In 1 patient who was bronchoscoped under Pentothal and ether anesthesia, there was only a 27 per cent fall of eosinophils four hours after the procedure. A standard dose of ACTH (25 mg.) produced a fall of 75 per cent in the same patient. It may be possible that anesthesia alone tends to block a normal pituitary-adrenocortical response and that a maximum stress may be needed to break through this inhibition.

The eosinophil levels were studied in 7 patients undergoing major operation under spinal anesthesia. In 4, a delay was observed in the rate at which the usual postoperative fall in eosinophils occurred. This delay was approximately equal to the duration of the effect of the spinal anesthetic. This finding suggests a transient block of adrenocortical stimulation in some patients by spinal anesthesia. Presumably this is related to the abolition of afferent sensory stimuli from the operative site.

Practical Applications

Postoperative Eosinophil Level as an Indicator of Adrenocortical Activity

An eosinophil level in itself means little. It is the *change* in level in the same patient following stress, epinephrine or ACTH that is significant and indicates the degree of adrenal functional reserve.[4] There is one situation, however, in which the eosinophil level is highly significant — that is, during the immediate postoperative period, from four to twenty-four hours after a major operation. A profound eosinopenia was found in all patients during this period. In patients with spinal anesthesia this eosinopenia is also present although it may be somewhat delayed. The finding of the eosinopenia is *in itself* an indication of greatly increased adrenal-hormone secretion. There is one exception to this rule: a very marked eosinopenia may occur in the presence of an aplastic bone marrow. In such a case, the production of eosinophils is inadequate, and the levels may be exceedingly low, even in the presence of a relatively inactive adrenal cortex.

The following case illustrates the use of the postoperative eosinophil levels to assay adrenocortical activity.

Case 1. O. L. (P.B.B.H. 9A411), a 29-year-old housewife, had a 48-hour history of pain in the right flank of sudden onset, accompanied by nausea and vomiting. She was referred to this hospital after the radiologic finding of a right renal calculus.

The temperature was 101°F., the pulse 130, and the blood pressure 60/40. She appeared acutely ill, but responded well to questioning. There was moderate spasm and tenderness at the right costovertebral angle. The urine gave a ++ test for protein, and the sediment contained many leukocytes, a few erythrocytes and no casts. The white-cell count was 6800, with 36 per cent adult and 42 per cent juvenile neutrophils. Shortly after admission, the patient underwent a ureterolithotomy under nitrous-oxide-induced ether anesthesia, lasting approximately 1 hour. During the operation, the blood pressure fluctuated between 120/60 and 100/50, the systolic pressure remaining at 100 or lower after operation. Because of this and the fact that the patient looked so poorly, the question of acute adrenocortical insufficiency was raised. An eosinophil count obtained 4 hours after operation was found to be 0 per cubic millimeter. This indicated that large amounts of adrenal steroids were being secreted and that the "shock-like" state was probably not due primarily to adrenocortical insufficiency. Although the blood pressure remained low, the patient subsequently recovered. Three days after operation, the eosinophil level had risen to 172 per cubic millimeter.

Conversely, during the immediate postoperative period, the finding of a normal or high eosinophil count points toward the diagnosis of adrenocortical insufficiency. Exception to this rule may exist in patients with allergic eosinophilia. These cases, either because of an excess production of eosinophils or because of a "steroid fastness" of the eosinophils themselves, may not respond to an increase in adrenal steroids by an eosinopenia such as is normally induced by a single injection of ACTH, by stress or by the direct intravenous administration of potent adrenal extracts.[4] Such patients may show a normal or elevated eosinophil level postoperatively although an actual fall in eosinophils may have occurred. We have not yet encountered, however, a patient with adequate adrenal glands who did not respond with an eosinopenia to the major stress of operation.

The following case illustrates the value of the postoperative eosinophilia in the diagnosis of adrenal insufficiency and demonstrates the role that the adrenal cortex plays in the production of the postoperative eosinophil fall.

Case 2. F. T. (P.B.B.H. OC455), a 55-year-old man, entered the hospital because of vague abdominal complaints and the finding by sigmoidoscopy of a small constricted

Table 2 (*Concluded*).

Patient	Operation	Postoperative day	ACTH Test† Before test	ACTH Test† After 4 hr.	ACTH Test† Change
			eosinophils/cu. mm.	*eosinophils/cu. mm.*	%
R. S.	Disk removal	4	145	46	−68
M. W.	Appendectomy	4	337	64	−81
E. G.	Appendectomy	4	59	23	−61
P. L.	Colectomy	3	105	58	−45
J. G.	Arthrotomy	3	59	10	−83

lesion of the sigmoid. General health had been excellent. Physical examination showed a well developed, healthy-appearing man. The blood pressure was 144/90. There was no abnormal pigmentation. The urine showed no protein, and the sediment contained no red or white blood cells or casts. The hemoglobin was 14.3 gm. per 100 cc., and the hematocrit 45 per cent. The white-cell count was 6650. The blood urea nitrogen was 11 mg. per 100 cc. Resection of a carcinoma of the sigmoid was carried out. The patient was anesthetized with Pentothal and ether. At the start of the operation, the blood pressure was 150/100, but it promptly fell and fluctuated around a level of 80/40 throughout the operation, which lasted approximately 4 hours. During the operation 1250 cc. of blood was administered. The patient recovered consciousness a few hours after operation, but the blood pressure remained low. Several electrocardiograms were taken, and they were normal. Eighteen hours after operation the low blood pressure persisted, and the

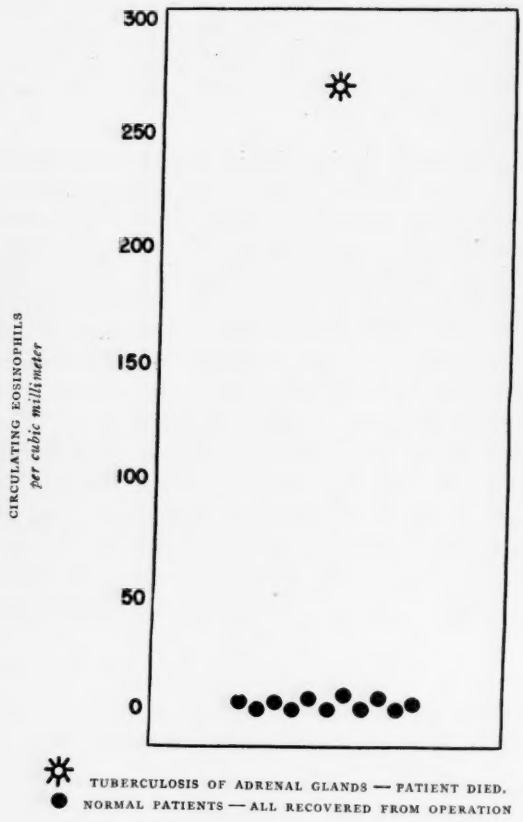

FIGURE 5. *Eosinophil Levels Five to Ten Hours after Major Operations.*

patient's clinical condition was poor. The diagnosis of adrenal insufficiency was entertained, and an eosinophil count was obtained. Figure 5 shows the patient's eosinophil level as compared with those of 12 normal patients counted at approximately the same time after their operation. With our previous knowledge as a background, the diagnosis of adrenal insufficiency suggested itself, although there was no evidence of increased pigmentation, no history of nausea or vomiting and no other clinical evidence of long-standing adrenocortical insufficiency. The patient received 50 cc. of Eschatin intravenously at once, with only slight improvement and no fall in eosinophil level. This was followed by 70 cc. of Eschatin intramuscularly over a period of 32 hours. In retrospect this amount of extract was totally inadequate. The patient died on the 2nd postoperative day.

Autopsy revealed bilateral apical fibrocaseous pulmonary tuberculosis and tuberculosis of the left kidney, healed. There was no evidence of coronary occlusion or myocardial infarction. From 60 to 80 per cent of adrenal tissue was replaced by fibrocaseous material. No tubercle bacilli could be demonstrated in the sections. Figure 6 shows a representative section of the right adrenal gland. Enough adrenal tissue

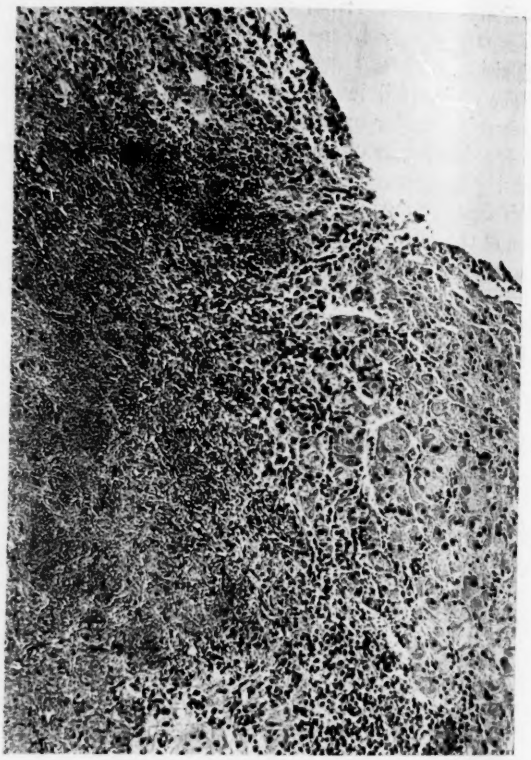

FIGURE 6. *Photomicrograph of a Section of the Right Adrenal Gland in Case 2, Showing Fibrocaseous Material Partly Replacing Adrenal Tissue.*

was apparently left to permit the patient to lead a normal life, but not enough either to protect him against the violent stress of surgery or to produce the usual eosinopenia.

Use of the ACTH Test Preoperatively

The question of adrenal insufficiency arises at times before an operation. The ACTH test furnishes an ideal way of answering such a question, because it is rapid and is essentially a functional test involving in its mechanism the very type of hormones that play a prominent part in the defense of the organism against stress.

CASE 3. L. D. (P.B.B.H. 7A439),* a 37-year-old housewife was first admitted to the hospital on December 31, 1947, with a 4 months' history of weight gain, pounding in the neck, frontal headaches, severe sweating episodes, amenorrhea and generalized aching. Physical examination revealed puffy obesity of the face and abdomen, a blood pressure of 206/108, purple striae over the arms, trunk and thighs and slight hirsutism. Examination of the blood showed a white-cell count of 15,100, with 81 per cent neutrophils, 13 per cent lymphocytes, and 6 per cent monocytes; the eosinophil

*Other aspects of the case have been reported elsewhere.[10]

count was 98 per cubic millimeter. The fasting blood sugar was 197 mg. per 100 cc., and the carbon dioxide combining power 29.9 milliequiv. and the serum chloride 94 milliequiv. per liter. The 24-hour urinary 17-ketosteroid excretion was 22.5 mg.; 11-oxysteroid excretion was 0.63 mg. per day (normal, 0.05 to 0.35 mg.). X-ray examination of the skull was negative.

A diagnosis of Cushing's syndrome was made, and a total of 4500 r was administered to the pituitary gland over a 3-week period. During the next 10 months, there was marked improvement in the symptoms and signs and a return of all laboratory tests toward normal. Ten months after the first admission, the patient was readmitted for routine follow-up study, and an irregularly enlarged uterus was found on pelvic examination. Operation was advised.

Because of the history of high x-ray dosage to the pituitary gland and the subsequent laboratory signs of progressive adrenocortical involution,[20] the possibility of pituitary insufficiency with possible secondary adrenal insufficiency was considered. Accordingly, an epinephrine and an ACTH test were performed. With epinephrine there was a 48 per cent fall in the eosinophil levels (control 114 per cu. mm.) and with ACTH a fall of 84 per cent. This made it appear probable that the patient's pituitary-adrenocortical system was intact and that she would be able to respond normally to operation. This impression was confirmed by her operative course. A panhysterectomy, lasting about 3 hours, was carried out, with the removal of a fibroid uterus. The patient withstood the operation well and had an uneventful recovery.

Case 4. M. B. (P.B.B.H. 9A272), a 47-year-old housewife, entered the hospital with a history of increasingly severe headaches of 2 years' duration. For 3 years there had been amenorrhea unassociated with hot flashes. Physical examination showed proptosis of the right eye and ptosis of the right lid, obvious bi-temporal hemianopsia, and a blood pressure of 154/100. Basic laboratory examinations were negative. The basal metabolic rate was − 7 per cent. An x-ray film of the skull disclosed erosion of the entire sella turcica, with complete obliteration of the sphenoid sinuses.

Operation was imperative owing to the visual impairment. Because of the probability of pituitary and possibly secondary adrenocortical insufficiency, epinephrine and ACTH tests were performed on the day prior to the operation. With epinephrine, there was a *rise* in the eosinophils from 105 to 131 per cubic millimeter. With ACTH there was a modest fall from 131 to 111 per cubic millimeter (−15 per cent). The diagnosis of pituitary-adrenocortical insufficiency was suggested by these findings. An attempt was made to stimulate the adrenal cortex ovenight by the administration of three doses of 25 mg. of ACTH each, but on the next day the eosinophils had *risen* to 294 per cubic millimeter, indicating that ACTH had failed to stimulate the production of cortical hormones. In spite of this, operation was undertaken. Shortly after the induction of ether anesthesia and prior to operative intervention, the patient became cyanotic and went into shock, from which she recovered only after the administration of large quantities of adrenal extract and 10 mg. of ephedrine intravenously. Operation was postponed. Six days later, after the patient had been treated with large amounts of ACTH and had shown laboratory and clinical evidences of adrenal stimulation (increased well being, fall in eosinophils to −75 per cent and a rise in urinary 17-ketosteroids from a level of 0.9 to a level of 8.9 mg. per 24 hours), a craniotomy with aspiration and biopsy of a cystic chromophobe adenoma of the pituitary gland was performed without incident. The patient had a stormy postoperative course but eventually recovered, with a return of the visual fields to normal and disappearance of the headaches.

In this case, the ACTH and epinephrine tests were useful in the diagnosis of adrenal insufficiency preoperatively, and the eosinophil levels helped in following closely the effects of ACTH therapy.

Discussion

The eosinophil is not of course the only blood cell affected by stress. After stress or the injection of ACTH, there is an increase of the neutrophils and a decrease of the lymphocytes.[2, 5] The changes in the neutrophils, however, are relatively short lived.

The lymphopenia occurring after stress has been described repeatedly.[1, 21] It has also been shown to be dependent upon increase in circulating 11-oxysteroids.[5]

There are several reasons why the eosinophils are more useful clinical indicators than the lymphocytes. With the method of Dunger,[18] they can be counted directly and quickly, without the need for a differential count. Their response to stress is more pronounced and more consistent than that of the lymphocytes and therefore easier to gauge. With continued adrenal steroid output, they remain depressed, whereas the lymphocytes after an initial fall soon rise again to their original levels.

The acute and transient rise of the eosinophil levels immediately after the onset of operation resembles the rise produced shortly after the injection of epinephrine; this action is apparently not dependent upon the adrenal cortex itself.[4] The curve of fall of the eosinophils during operation is analogous in shape and duration to that which takes place after the injection of ACTH; it is probably initiated by the increased secretion of the patient's own ACTH, which in turn leads to the secretion of the 11-oxysteroids by the adrenal glands. Eosinopenia after major surgical procedures has also been found by others.[22]

The "third-day eosinophilia" suggests that there is at this time a relative decrease in production of 11-oxysteroids, which is possibly due to the diminution of stress, adrenocortical exhaustion or pituitary deficiency or inhibition. A positive response to ACTH at this time effectively eliminates primary cortical exhaustion and by the same token refractoriness of the eosinophils as causes of the third-day eosinophilia. The lack of response to epinephrine suggests that, at least in some cases, there is at this time a transient pituitary deficiency or inhibition. In most cases, however, the diminution of stress as indicated by clinical improvement seems in some way to cause the third-day eosinophilia.

The postulation of a relative decrease in 11-oxysteroid production during the first three or four postoperative days does not contradict the well proved finding of an absolute increase in 11-oxysteroid production for as much as ten to fifteen days after a major operation, as suggested by an increased excretion of 11-oxysteroid in the urine.[12, 14]

Summary

The changes in the circulating level of eosinophils following major surgical operation are outlined, and the possible relation of these changes to altered adrenocortical function is discussed.

The measurement of the fall in eosinophils after the injection of 25 mg. of ACTH before operation is a good index of the capacity of the adrenal cortex

to excrete 11-oxysteroids and furnishes a good means of preoperative prognosis.

In the presence of normal adrenocortical activity, there is an almost complete disappearance of circulating eosinophils during the first twenty-four to forty-eight hours after a major operation.

The finding of an eosinopenia during the same period is in itself evidence of increased adrenocortical activity.

Conversely, the finding of a normal or high eosinophil level during the first twenty-four to forty-eight hours after an operation suggests adrenocortical insufficiency.

There is usually a sharp rise of the eosinophil level on the second to the fourth postoperative day, associated with clinical improvement. This "third-day eosinophilia" is associated with return of normal adrenocortical reserve.

The response of the eosinophils to ACTH during the postoperative period provides a rapid and useful means of assaying adrenocortical reserve, whereas the epinephrine response may give equivocal results at this time.

We are indebted to Drs. Hartwell Harrison, J. Englebert Dunphy and Donald D. Matson for facilitating the studies on Cases 1, 2 and 4 respectively and to Dr. Daniel M. Hays for the report on the pathological findings and the preparation of the photomicrograph.

Addendum. A modification of Randolph's eosinophil stain may also be used[23]:

Phloxine	0.05 gm.
Propylene glycol	50.0 cc.
Distilled water	50.0 cc.

This fluid does not require refrigeration and has a low rate of evaporation and little tendency to destroy eosinophils. As a consequence the pipette may be shaken thoroughly, as in an ordinary leukocyte count, and the cells may be allowed to remain in contact with the fluid until the actual count is performed, an obvious advantage if capillary blood is to be used. The only disadvantage of the stain is that it requires fifteen minutes for complete staining of the eosinophils.

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ANAPHYLACTIC REACTION FOLLOWING INJECTION OF HEPARIN*

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THE occurrence of reactions following the use of anticoagulants in the management of patients with myocardial infarction, pulmonary infarction and thrombophlebitis and after vascular surgery has served to emphasize the potential danger of these drugs. In general, the reactions either have been local (pain, abscess formation, hematoma, necrosis) or have resulted from overdosage, with bleeding into various parts of the body. Little has been written concerning allergic reactions to anticoagulants, particularly to heparin. Thus, Murray[1] reported on the use of heparin in 440 patients without the occurrence of anaphylaxis. Crafoord and Jorpes[2] analyzed the results of some 30,000 doses of heparin in Sweden and reported, without further comment, only 1 case of anaphylaxis.

The possibility of sensitization to heparin after repeated injections was first considered in the 1920's, when it became apparent that the drug might prove useful as an anticoagulant. Reed and Lamson,[3] in 1926, gave intravenous injections of varying amounts of a crude heparin preparation to dogs and rabbits and observed no reactions after a single dose. After intraperitoneal injections of the same material, they noted, in a few cases, symptoms characterized by prostration and weakness occurring after the first injection. Testing these animals two or three weeks later by the scratch and intracutaneous methods, they failed to elicit local reactions of sensitivity. A second injection of a comparable dose of heparin was then given both sets of animals and in most cases caused no reaction, although in a few, symptoms suggestive of anaphylaxis seemed to have occurred. The authors interpreted their observations as suggesting either that a protein component of the heparin preparation used may have sensitized certain susceptible animals, or that heparin possessed toxic products of an unknown nature. With the use of more highly purified material, however, no reactions were noted after either injection. Further studies on cross reactions between animal serum and the heparin solution disclosed no evidence of specific or nonspecific antigenic properties of heparin.

De Takats,[4] in 1943, described three distinct types of reactions in patients given intravenous injections of 10 mg. of heparin. When the coagulation time by the capillary tube method rose above 7½ minutes, he classified the patients as hyper-reactors. Eight of 87 subjects fell into this group, 7 of whom exhibited flushing of the face, dyspnea, choking, constriction of the chest and faintness. De Takats made the following observation:

> That these clinical symptoms should be accompanied by a prolongation of the coagulation time is significant in the light of a similar clotting phenomenon in anaphylactic reaction. . . . If heparin is normally secreted into the blood stream, could sensitization occur to the endogenous product? This question needs further study.

More recently, Grolnick and Loewe[5] reported the presence of reagins for heparin in a patient under treatment for subacute bacterial endocarditis who manifested fever and urticaria while receiving combined penicillin and heparin therapy. Four factors were considered as possible causes for the reaction — namely, penicillin, heparin, phlebitis (which complicated the patient's course) and the infection itself. Inasmuch as the patient had several courses of combined penicillin and heparin therapy with a more rapid and more pronounced reaction to each course, it was concluded that the symptoms were due to an acquired drug sensitivity of the serum-disease type. Penicillin alone caused no reaction, and scratch, intradermal and ophthalmic tests were negative. No reagins or precipitins to penicillin could be demonstrated, although it was recognized that such findings do not generally occur with drug hypersensitiveness. On the other hand, skin tests to heparin were persistently positive, and reagins to this drug were demonstrated by the passive transfer method. Complicating the situation to a considerable degree, however, was the fact that reagins to beef serum and beef lung, as well as to heparin solution, were present. Positive skin tests to all three were also noted. Thus, it was impossible to determine whether the protein fraction of the solution or the heparin itself was responsible for the results obtained.

Cortes, Grolnick and Loewe[6] also undertook studies to determine whether heparin was capable of inducing manifestations of anaphylaxis in animals. Guinea pigs were given 20 mg. of heparin intra-abdominally and killed about four weeks later. No evidence of anaphylactic contraction was noted in intestinal strips by the Schultz–Dale technic. A second group of pigs was then given a series of two injections, one week apart, by the intra-abdominal route, the dosage being 20 mg. each time. Again Schultz–Dale studies four weeks later gave negative results. The authors concluded, therefore, that their experiments had failed to reveal evidence of anaphylactic sensitivity in the guinea pig after attempts at sensitization with heparin.

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Within the past year, 3 cases of probable allergic reactions to heparin have been observed in the Barnes Hospital. One of the patients exhibited urticaria, and the other 2 had anaphylactic reactions, 1 of which almost terminated fatally. The latter case is the subject of the present report.

Case Report

H. J. H. (B. H. 161025), a 54-year-old barber, was admitted to the ward medical service on July 6, 1948, complaining of pain in the chest of 6 hours' duration. Except for minimal urinary difficulty (slight hesitancy and frequency), the patient had been well until about 6 months before admission, when he noted the onset of easy fatigability and occasional soreness in the left arm while he was cutting hair. Nevertheless, he was able to do his daily work without difficulty. The day before admission, he had driven some 200 miles with only slight fatigue. About 9 a.m. on the day of admission he became aware of a sticking sensation high in the chest, substernally, which forced him to stop work momentarily. He took sodium bicarbonate, with no relief, and returned to work. The discomfort gradually moved down into the chest, remaining substernally, became much more severe over the next hour and assumed a crushing character. As the pain reached its maximum intensity, the patient noted its radiation to the interscapular area, both shoulders, elbows and wrists, being more marked on the right side. There was profuse sweating, but no nausea, vomiting, faintness or dyspnea. Because the pain persisted, he entered another hospital, where he was given an injection of what he was told was epinephrine, with no relief of his discomfort. Consequently, he came to Barnes Hospital for further treatment.

The past history was irrelevant except for the presence of gonorrheal infections at the age of 16 and 22. In 1916, at the age of 22, a penile lesion developed and was treated with one injection of arsphenamine. Twelve years later, the patient was treated for several weeks with mercury, bismuth and neoarsphenamine. Blood and cerebrospinal-fluid tests for syphilis are said to have been repeatedly negative during this time. There was no history of rheumatic fever, high blood pressure, previous heart trouble, cough, orthopnea, paroxysmal dyspnea, angina, dyspnea on effort or ankle edema. He had never received any digitalis. No history of allergy could be elicited, and as far as the patient was aware, he had never received any heparin prior to the present admission. Both parents were living at the age of eighty-eight, although the father was said to have "heart trouble." The patient smoked about 1½ packages of cigarettes a day and took "an occasional drink."

Physical examination revealed an acutely ill, heavy-set man who was sweating profusely. His color was good. Both pupils were pin point (he had received morphine sulfate in the emergency room), and the fundi were not visualized. The conjunctivas were slightly injected. There was no venous distention. The trachea was in the mid-line, and there was no tug. Cardiac examination revealed a heart of normal size with the point of maximum impulse 9 cm. from the midsternal line in the fifth interspace. The heart sounds were of good quality but somewhat distant. The first sound at the mitral area was split, and the second aortic sound was louder than the pulmonic. A Grade I systolic murmur was heard at the apex. No diastolic murmurs were audible. No gallop rhythm or friction rub was noted. The lungs were normal except for a few dry crackles at each base. Abdominal examination was negative. There was no ankle edema. Both dorsalis-pedis arteries were easily palpable. Reflexes were equal bilaterally.

Table 1. *Scratch Tests on Patient and Control Subject.*

Material	Test Route	Patient's Initial Test		Patient's Repeat Test		Control Subject
		Wheal	Erythema	Wheal	Erythema	
		mm.	mm.	mm.	mm.	
First heparin solution:						
Undiluted	Scratch	—	—	2 x 5	0	Negative
1:100	Intradermal	—	—	15 x 10	20 x 20	Negative
1:1000	Scratch	9 x 9	20 x 20	—	—	—
1:1000	Intradermal	8 x 7	23 x 30	8 x 7	25 x 15	—
Second heparin solution:						
Undiluted	Scratch	—	—	Negative	Negative	Negative
1:100	Intradermal	13 x 15	45 x 50	9 x 6	25 x 20	Negative
1:1000	Scratch	0	10 x 10	—	—	—
1:1000	Intradermal	—	—	6 x 5	20 x 20	—
Diluent	Intradermal	—	—	Negative	Negative	Negative
Beef*	Intradermal	—	—	11 x 9	14 x 12	Negative
Pork*	Intradermal	—	—	7 x 8	15 x 15	Negative

*10,000 protein nitrogen units per cubic centimeter.

Table 2. *Tests Performed on Patient Ten Months after Initial Reaction and on Control Subject.*

Test Route and Dilution	Patient's Test with First Heparin Preparation		Patient's Test with Second Heparin Preparation		Control-Subject Tests	
	Wheal	Erythema	Wheal	Erythema	First heparin preparation	Second heparin preparation
	mm.	mm.	mm.	mm.		
Scratch:						
(Undiluted)	Negative	Negative	Negative	Negative	Negative	Negative
Intradermal:						
(1:10,000)	Negative	Negative	Negative	Negative	Negative	Negative
(1:1000)	Negative	Negative	4 x 4	0	Negative	Negative
(1:100)	Negative	Negative	10 x 6*	15 x 15	Negative	Negative
(1:10)	6 x 6*	20 x 20	8 x 8*	18 x 18	Negative	Negative

*Irregular borders.

The temperature was 37.5°C. (99.5°F.), the pulse 68, and the respirations 24. The blood pressure was 176/96 in the right arm and 170/92 in the left.

Examination of the blood showed a red-cell count of 5,550,000, with a hemoglobin of 17 gm., and a white-cell count of 20,100, with 2 per cent basophils, 1 per cent juvenile, 7 per cent stab and 71 per cent segmented forms, 17 per cent lymphocytes and 2 per cent monocytes. Examinations of the urine and stool were negative, as was a serologic test for syphilis.

The patient was given 10 mg. of morphine sulfate on admission, with some relief of the pain. An electrocardiogram revealed a sinus rhythm of 80, normal PR and QRS intervals, low voltage of the QRS complex in Lead 1 and moderate slurring in all leads. The main deflection of the QRS complex was upright in Leads 1 and down in Leads 2, 3 and CF_4. The T waves were upright in the limb leads and diphasic in Lead CF_4. There was ST-segment elevation in Lead CF_4. A diagnosis of anterior myocardial infarction was made, and the patient was put to bed, morphine being administered as needed and anticoagulant therapy being started. The patient received his first injection of 50 mg. of heparin about 4 hours after admission, being given 5 cc. of sodium heparin solution (10 mg. per cubic centimeter) intravenously over a period of 2 minutes. About 60 seconds after the needle had been withdrawn from the vein, he suddenly began to gasp for air, became deeply cyanotic, broke out into a drenching sweat, cried out that he was unable to breathe and thrashed wildly about. The pulse and blood pressure were both unobtainable. The heart sounds could not be heard. Examination of the chest demonstrated tight asthmatic breathing, with almost no respiratory exchange despite vigorous thoracic motion. A vivid red macular rash appeared over the entire body. Because of the urgency of the situation, 0.2 cc. of epinephrine was given subcutaneously, with oxygen by mask, and shortly thereafter oral administration of Benadryl was begun. Within 5 minutes his color improved, the respirations became slower and less labored, and the heart sounds were audible although distant. A few dependent rales were present, but breath sounds were normal. Cardiac irregularity was transiently noted, but a normal sinus mechanism soon became established. Three hours later the patient's color was good, the blood pressure was 130/80 in each arm, the pulse rate was 76, and the respirations 18. Dicumarol therapy was then instituted, with an initial dose of 300 mg. The rash noted above assumed a blotchy, erythematous character and disappeared within several hours. Later, when the patient had recovered sufficiently to talk, he described the sensations he had experienced while getting the injection of heparin. He first felt a prickly, tingling sensation in his extremities, then an intense burning and itching of his eyes and body and finally a terrifying inability to get his breath.

The subsequent course was relatively uneventful. For about 4 weeks there was an autonomic imbalance between the right and left sides of the body, extending from the level of the fourth or fifth cervical segment to the midthigh region. The skin on the right side of the body in this area was warm and dry, whereas on the opposite side, it was cold, moist and clammy. The blood pressure was 120/75 in the right arm and 112/92 in the left. The pulse was definitely weaker on the left. There were no other neurologic signs. The prothrombin time was kept at suitable levels without difficulty, and the patient gradually improved in spirit and well-being. The temperature reached a maximum of 38.2°C. (100.8°F.) on the 3rd hospital day, gradually returning to normal. The blood pressure became normal in both arms, and the sedimentation rate, which had reached a maximum of 1.2 mm. per minute 4 days after admission gradually returned to normal after 4 weeks. The white-cell count dropped to 12,000 on the 3rd day and was normal a week later. X-ray study of the chest was negative. Repeated electrocardiograms showed changes typical of an anterior myocardial infarction.

After discharge, the patient was followed for almost a year. The blood pressure was stabilized at 120/80 in both arms, with no differences in skin temperature on the two sides of the body. Except for occasional episodes of angina, he had suffered no residual effects from his acute illness.

TABLE 3. *Passive-Transfer Studies.**

Dilution	Patient's Serum of 8/3/48				Patient's Serum of 6/14/49				Control Series	
	Size of wheal	Character of wheal	Size of erythema	Character of erythema	Size of wheal	Character of wheal	Size of erythema	Character of erythema	Wheal	Erythema
	mm.		*mm.*		*mm.*		*mm.*		*mm.*	*mm.*
First heparin preparation:										
1:100	7 x 7	—	20 x 15	—	0	—	0	—	0	0
1:10	10 x 9	Irregular borders	35 x 25	Moderately intense	0	—	0	—	0	0
Undiluted	—	—	—	—	4 x 3	—	10 x 10	Scattered, very faint	0	0
Second heparin preparation:										
1:100	7 x 7	Irregular borders	25 x 20	Moderately intense, with itching	4 x 5	—	10 x 10	Scattered, very faint	0	0
1:10	7 x 7	Irregular borders	30 x 30	Intense, with itching	5 x 5	—	20 x 20	Scattered, faint	0	0
Undiluted	—	—	—	—	4 x 5	—	20 x 30	Faint	0	0
Beef:										
10,000 protein nitrogen units per cubic centimeter	5 x 4	—	35 x 40	Itching	3 x 3	—	8 x 12	Scattered	0	0
Pork:										
10 000 protein nitrogen units per cubic centimeter	3 x 3	—	40 x 50	Itching	—	Slight induration	0	—	0	0

*0.05 cc. of serum injected intracutaneously; 0.02–0.03 cc. of test solution injected intracutaneously 48 hr. later. Negative reactions are indicated by "0."

Immunologic Studies

Because of the severe reaction exhibited by this patient after the injection of heparin, an attempt was made to test the solution used, as well as the patient, for further information regarding the mechanism involved. Heparin from the same vial was subjected by the manufacturer to the standard tests for depressor substance (Council of Pharmacy and Chemistry of the American Medical Association). No depressor response in anesthetized cats was noted, indicating less depressor substance than 0.1 microgm. of histamine base per 0.2 cc. of the

sample. Since the patient received only 5 cc. of the solution, it seems unlikely that histamine or other depressor substances could have been responsible for the reaction noted.

Further studies were then undertaken with two different commercial heparin solutions, prepared from different animal sources. The first preparation was extracted from pork liver and was the product used in this case. The second solution was prepared from beef lung and was thought to be free of extraneous antigenic material, although the possibility of traces of contaminating protein could not be ruled out.

Scratch tests were performed with the first heparin solution in a dilution of 1:1000 (10 mg. per cubic centimeter). A 1-cm. wheal with irregular borders surrounded by a zone of erythema extending an additional centimeter developed within fifteen minutes (Table 1). The second preparation, used in the same dilution, gave only a 1-cm. zone of erythema. In intracutaneous tests a 1:1000 solution of the first solution of heparin yielded approximately a 1-cm. wheal and a 2.5-cm. surrounding erythema, whereas a 1:100 solution of the second preparation gave a slightly greater wheal and surrounding erythema (1.3 cm. and 4.5 cm., respectively). Repeat studies with intracutaneous tests using varying concentrations of the two products gave identical erythema and wheal reactions, but no reaction whatsoever in a normal patient selected as a control. The diluent gave no reaction in either subject. Intracutaneous tests with beef, pork and lamb extracts gave slight but definite reactions (1-cm. wheal and 0.3-cm. surrounding erythema).

Further direct studies were not possible because of the patient's desire to leave the hospital, although serum was obtained for passive-transfer studies. On June 13, 1949, about ten months after the initial reaction, the patient was retested by both the scratch and intradermal technics to the concentrations of heparin indicated in Table 2. Scratch tests to both heparin solutions were negative, whereas definite wheal and erythema reactions were present with 1:10 dilutions of the first heparin preparation and in 1:100 dilutions of the second.

TABLE 4. *Neutralization Studies — Passive-Transfer Method — on Control Subject.**

TEST SOLUTION	REACTION† AT PASSIVE-TRANSFER SITE WITH SERUM OF 1948				
	FIRST HEPARIN PREPARATION ADDED	SECOND HEPARIN PREPARATION ADDED	BEEF ADDED	PORK ADDED	SALINE SOLUTION ADDED
Beef (10,000 protein nitrogen units per cubic centimeter)	+	0	+++	++++	+++++
Pork (10,000 protein nitrogen units per cubic centimeter)	0	0	±	+++	+++++
First heparin preparation (undiluted)	±	±	++++	++++	+++++
Second heparin preparation (undiluted)	±	0	++	++++	+++++

*0.25 cc. of serum + 0.25 cc. of antigen or saline solution, allowed to remain in refrigerator overnight; 0.05 cc. of solution injected intradermally in recipient and sites tested 48 hr. later with 0.02–0.03 cc. of test solution.

†Reactions are indicated as follows:

\+ = wheal without erythema.
++ = smooth wheal with slight erythema.
+++ = irregular wheal with moderate erythema.
++++ = very irregular wheal with intense erythema and itching.
+++++ = somewhat more marked reaction than ++++.
0 = negative.

Passive-transfer studies were then carried out on serum taken from the patient on August 3, 1948, and again on June 13, 1949 (the former having been kept in the frozen state for the ten-month period). A test subject was given intradermal injections of 0.05 cc. of the patient's serum, and the sites were tested forty-eight hours later with 0.02 to 0.03 cc. of the antigen. These tests resulted in rather striking reactions to the various dilutions of the heparin solutions used, although the control series yielded no reactions (Table 3). With the serum taken shortly after the patient's reaction to the heparin, wheals with irregular borders and extensive surrounding erythema resulted. The tests showed a graded response with dilution, little difference between the two preparations of heparin being observed. When the serum taken ten months later was tested, much less striking, but still definite, reactions were obtained. The same difference in reactivity of the two serums was noted when the passive-transfer sites were tested with pork and beef protein.

In an effort to determine whether the reactions noted when heparin was injected into the passive-transfer sites were due to the contaminating protein or to the heparin itself, a series of neutralization studies was performed, 0.25 cc. of the patient's serum being mixed with 0.25 cc. of both preparations of heparin, as well as with beef and pork protein extracts (10,000 protein nitrogen units per cubic centimeter). Each mixture was permitted to remain overnight in the refrigerator and was then injected intradermally (0.5 cc.) into the test subject. The passive-transfer sites were tested forty-eight hours

later with both preparations of heparin and with beef and pork protein. The results obtained are listed in Table 4. It will be noted that in general the 1948 serum was far more reactive than the 1949 serum. Heparin-neutralized serum was unreactive to any of the antigens injected into the passive-transfer sites, whereas the serum neutralized with pork and beef gave reactions with nearly all the antigens used.

TABLE 4 (*Concluded*).

TEST SOLUTION	REACTION† AT PASSIVE TRANSFER SITE WITH SERUM OF 1949					CONTROL SERIES
	FIRST HEPARIN PREPARATION ADDED	SECOND HEPARIN PREPARATION ADDED	BEEF ADDED	PORK ADDED	SALINE SOLUTION ADDED	
Beef (10,000 protein nitrogen units per cubic centimeter)	0	0	0	0	+	0
Pork (10,000 protein nitrogen units per cubic centimeter)	0	0	0	0	0	0
First heparin preparation (undiluted)	0	0	0	+	+	0
Second heparin preparation (undiluted)	±	++	±	±	0	0

DISCUSSION

As in previous cases of reaction following the use of heparin, the exact nature of the sensitizing antigen remains obscure. Whether the reaction was caused by a sensitivity to heparin or to contaminating proteins in the extract could not be definitely determined. The fact that the patient reacted less, on direct skin test, to the concentrated extracts of beef and pork protein than to the heparin solution suggests that heparin itself may have been the responsible agent. Also, the patient gave positive skin tests to both heparin solutions, despite the fact that they came from two different animal sources. The passive-transfer data, likewise, were suggestive but not conclusive. Reagins to heparin solution and to both pork and beef were demonstrated. Attempts to neutralize these antibodies met with equivocal results. The passive-transfer sites containing serum previously treated with heparin failed to react with either of the two heparin preparations or with beef or pork protein. On the other hand, pork-serum and beef-serum mixtures reacted not only with the heparin solutions but also with pork and beef antigens. The evidence obtained in the case reported suggests, but does not prove, hypersensitivity to heparin itself.

SUMMARY

The literature concerning allergic reactions to heparin is briefly reviewed.

A case of anaphylactic reaction following an injection of heparin solution is reported.

Immunologic studies suggesting a true hypersensitiveness to heparin are presented and discussed.

I am indebted to Dr. Samuel C. Bukantz and Miss Mary Johnson for their valuable suggestions and help in carrying out the various procedures described.

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THE SURGICAL TREATMENT OF ULCERATIVE COLITIS*

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THE treatment of ulcerative colitis is primarily medical. Experience has shown, however, that at least 25 per cent of patients with ulcerative colitis require surgical intervention,[1, 2] to preserve life, for the relief of chronic invalidism or to treat one of the frequent complications of this disease such as perforation, arthritis or malignant degeneration in the diseased colon.

From 1927 to January, 1949, 263 patients with ulcerative colitis were operated on. An ileostomy was carried out on 216 and partial colectomy on 59 patients, and 148 patients had a complete colectomy in addition to ileostomy. The following remarks are based upon this experience.

INDICATIONS FOR SURGERY

Acute Fulminating Ulcerative Colitis

No manifestation of ulcerative colitis calls for closer co-operation between the internist and the surgeon than the acute fulminating form of this disease. These patients may die from overwhelming sepsis within a few days. The mortality is high from either medical or surgical treatment. Nevertheless, experience has shown that many patients who fail to respond to conservative treatment may be saved by an ileostomy with complete diversion of the fecal stream. The delay of even a few days in the acceptance of operation may be fatal.

Hemorrhage

An early decision regarding the advisability of surgical intervention may be necessary in patients who have persistent, severe bleeding. If the bleeding is profuse and fails to respond to conservative measures, ileostomy must be considered as a means of preventing a fatal hemorrhage. The risk of more extensive surgery in a patient with ulcerative colitis who is actively bleeding is considerable, but occasionally defunctionalization of the colon by an ileostomy is not sufficient to stop the bleeding and resection of the most severely diseased segment of colon, usually the rectum and rectosigmoid, must be carried out. An emergency abdominoperineal resection was necessary to control bleeding in several of these patients. One patient who had active bleeding from her entire colon required a one-stage complete colectomy and abdominoperineal resection to stop a persistent hemorrhage.[3]

Chronic, intermittent bleeding of a moderate degree is much more common in ulcerative colitis and, resulting as it frequently does in chronic anemia, often becomes, indirectly, an indication for surgical intervention.

Perforation

Ulcerative colitis may lead to perforation of the diseased bowel, and operation is necessary for the treatment of this complication. Fortunately, as a result of adhesions secondary to the extensive inflammatory process in the colon, acute perforation into the free peritoneal cavity is rare. When it does occur it is usually fatal, and treatment is limited to supportive measures, transfusions and the antibiotics. If the patient survives the generalized peritonitis, an ileostomy should be carried out as soon as his condition permits. Residual abscesses in the pelvis should be drained by colpotomy or proctotomy.

Subacute or chronic perforation is more common, and may result in localized abscess formation or the formation of fistulas between loops of colon, between colon and small bowel or between colon and vagina. Not only are these complications indications for surgery but also the procedure, in practically every case, must be directed toward the cause of the complication; it consists of ileostomy followed by colectomy. Local operations, even for such common complications as fistula in ano, give poor results in patients with ulcerative colitis. The surgical incision heals poorly, if at all, and not infrequently rectal incontinence results. Once rectal incontinence has occurred, either spontaneously or as the result of an operative procedure, the patient should be advised to have an ileostomy. No type of local treatment will relieve his incontinence, and he will be infinitely more comfortable with an ileostomy and a well fitting ileostomy bag.

Infectious Arthritis

The onset of arthritic pain in a patient with ulcerative colitis should always raise the question of surgical intervention. If the infectious focus is removed by colectomy before structural changes occur in the involved joints, the pain and swelling are dramatically relieved. If this complication is allowed to persist, it may result in severe, crippling arthritis.

Obstruction

Chronic ulcerative colitis is characterized by periods of exacerbation followed by healing. In patients with extensive disease, there may be marked fibrosis and contraction of the diseased colon. This

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usually occurs late in the course of the disease, and it may involve one segment of the colon or the entire large bowel and rectum. It presents the striking appearance seen on barium-enema examination that is termed "lead-pipe colon." These patients do poorly on medical management. Not only is ileostomy indicated but also it must be considered as permanent, and it is usually followed by resection of the diseased bowel. Even if complete healing should follow the ileostomy, further fibrosis of the bowel wall will occur, with further narrowing of the lumen so that a return to normal function of the colon is impossible.

Malignant Degeneration

Another complication that may result from long-standing ulcerative colitis is malignant degeneration in the diseased colon. The longer these patients are followed, the more frequently this complication is encountered. It has been estimated that carcinoma occurs in 5 to 8 per cent of patients with ulcerative colitis, but in patients who have had the disease eight years or more an incidence of malignant degeneration between 25 and 30 per cent has been found.[4]

Carcinoma tends to occur at a relatively early age in patients with ulcerative colitis. It spreads rapidly, and the prognosis is poor. A sudden onset of bleeding without associated exacerbation of the other signs of the disease in a patient with long-standing ulcerative colitis may indicate the development of cancer. This complication may occur even when patients are apparently improving. The only hope of detecting malignant change at a stage when cure can be effected is by a careful, prolonged follow-up study. Any patient with chronic ulcerative colitis whose colon has not been removed should have repeated checkup examinations. A sigmoidoscopic examination should be included, since the malignant lesion may arise in the rectosigmoid region, where it could be missed on a routine barium-enema study.[5] A patient who has had the disease eight years or more and who requires an ileostomy should also have a *total* colectomy, including abdominoperineal resection, because of the danger of this complication.

Intractability

The last but the most frequent indication for surgical intervention in ulcerative colitis is intractability to medical management. Here, the indications are less clearly defined, again emphasizing the necessity for close co-operation between the gastroenterologist and the surgeon in the treatment of patients with this disease. If a patient, in spite of careful medical management, is unable to carry on a reasonable degree of social and economic activity as a result of poor nutrition, weakness, abdominal or rectal discomfort or uncontrollable diarrhea, he should be advised to have an ileostomy with or without a subsequent colectomy. To be more specific, it is believed that surgical treatment should be considered and usually advised for any patient who is no longer able to continue productive work and who is incapacitated for three months out of the year.[6]

Type of Surgery Indicated

Appendicostomy, cecostomy and colostomy are of little value in the treatment of ulcerative colitis. We have had no experience with the use of vagotomy as suggested by Dennis et al.[7] If it is to be used for the routine treatment of all patients with ulcerative colitis it must be evaluated in the light of the spontaneous remissions and exacerbations that are characteristic of this disease. If it is to be of value in the treatment of patients with extensive disease, of which I have been speaking, it must be as effective as ileostomy and colectomy.

The surgical procedures at present employed are ileostomy and subtotal and total colectomy.

In the small group of patients in whom the disease is limited to one segment of the colon, such as the right side, subtotal colectomy with restoration of intestinal continuity may be employed. In spite of care in selecting these patients and in spite of what was considered to be a wide resection of the diseased bowel, the poorest results have occurred in this group of patients. The difficulty lies in determining the exact point in the colon where the disease begins and ends. If any diseased colon or terminal ileum remains, the inflammatory process will involve the area of anastomosis, and symptoms will recur.

Most patients with chronic ulcerative colitis in whom surgery is indicated require an ileostomy. This is followed by two-stage total colectomy and abdominoperineal resection, depending upon the extent of the disease, the persistence of symptoms such as chronic anemia, malnutrition and infectious arthritis, or the development of a complication such as perforation or cancer.

In the last few years the first stage of the colectomy has occasionally been carried out, removing the colon to the mid-transverse or mid-descending segment at the same time that the ileostomy is established. This combined procedure should be limited to patients who are in the chronic cicatricial stage of the disease if the present low operative mortality in ulcerative colitis is to be maintained.

In a very few patients who have had an ileostomy it will be possible to close the ileostomy and reestablish intestinal continuity. Before this is done every effort should be made to determine that the colon is actually completely healed and able to resume its normal function; otherwise, the symptoms of ulcerative colitis will promptly recur. The following criteria for closure of an ileostomy have been used: the patient must have had a complete remission of symptoms for a year or more; the

rectum and rectosigmoid must be negative to sigmoidoscopic examination; and the barium enema must demonstrate an adequate lumen in the remainder of the colon. Following these criteria, it has been possible to close the ileostomy in only 10 per cent of patients with ulcerative colitis, and in half of this small group it has been necessary to reestablish the ileostomy because of reactivation of the disease. If ileostomy is carried out earlier in the course of ulcerative colitis before structural changes occur in the diseased colon, it will probably be possible to restore intestinal continuity[6] in a larger number of cases after healing has occurred. Nevertheless, the chronicity of this disease is amazing,[8] and reactivation may occur after the colon has been defunctionalized for many years.

Ileostomy

Since an ileostomy in a patient with ulcerative colitis is usually permanent, any technical point in its construction that will aid in its proper functioning or will decrease the incidence of complications to which such patients are subject has a direct bearing on their future health and happiness.

The development of a well fitting ileostomy bag that permits an airtight connection between the bag and the abdominal wall has been the outstanding factor in the restoration of these patients to normal social and economic activity.

Thus, the ileostomy incision, particularly the point at which the ileum is to be exteriorized, is important. If the ileostomy is made too close to the umbilicus, the costal margin, the anterosuperior iliac spine or the symphysis pubis, the ileostomy bag will not fit securely, and odor and fecal content will escape, resulting in considerable physical and mental distress for the patient. A small right-rectus-muscle-splitting incision, bringing the ileum out 3.5 cm. below and 2.5 cm. to the right of the umbilicus, at approximately the most convex portion of the lower abdominal wall, is preferred.

The abdominal cavity is not explored since even gentle handling of the diseased colon is likely to result in some degree of peritonitis. Since ulcerative colitis frequently involves the terminal ileum, it is important to select a point at least 25 to 30 cm. proximal to the ileocecal valve and proximal to any involved ileum for the establishment of the ileostomy. After the division of the bowel and the mesentery, the mesentery of the functioning loop is again divided for a short distance, at right angles to the vertical incision, between the second and third vascular arcades. This prevents a curvature of the ileostomy, which might complicate its subsequent management.

If the patient is seriously ill, the distal and proximal loops of ileum are simply brought out through the original incision, with the functioning loop below so that its contents will not spill over into the defunctionalized colon. If the patient's condition permits and the disease is such that a subsequent colectomy will probably be indicated, we prefer to bring the distal nonfunctioning loop of ileum out through a stab wound above and to the right of the ileostomy incision, where it can be incorporated in the oblique or transverse incision used for the colectomy.

An ileostomy in a patient with ulcerative colitis is notorious for its tendency to prolapse or retract,[9] and careful fixation of the ileum to the abdominal wall is one of the most important steps in the operative procedure. Sutures cannot be placed in the bowel wall itself. To do so is to invite a fistula, which will interfere with, if not completely prevent, adequate fixation of the ileostomy bag. The mesentery of the ileum is carefully fixed to the peritoneum of the abdominal wall by a row of interrupted sutures on each side. The end of the ileum should be brought 3.5 to 5 cm. above the skin level so that, even after shrinkage occurs, it will empty its contents directly into the bag, well away from the surrounding skin. Ileostomies are not surrounded with skin grafts. If the mucosa is allowed to grow down and unite with the skin, a less rigid ileostomy will result. We have never closed the distal or nonfunctioning loop of ileum and dropped it back into the peritoneal cavity. Healing in the diseased colon results in fibrosis of the bowel wall, with a decrease in the size of the lumen. Stenosis may occur at any point and may be followed by perforation of the closed loop thus produced. When the transverse or descending colon is divided during the first stage of the colectomy, the distal loop is always exteriorized through a stab wound, where the loop can be incorporated in the incision for the subsequent abdominoperineal resection. Bowel wall, the seat of ulcerative colitis, heals poorly, and to close this distal loop and leave it within the peritoneal cavity is to risk leakage and peritonitis.

When the incision has been closed and the dressings applied, the obstructed ileum is decompressed with a large catheter inserted in the open end, passed beneath the peritoneal layer and secured by a purse-string suture. This will drain satisfactorily for four or five days without soiling of the dressing or wound. The dressing is not wound around the ileostomy lest constriction result. The first dressing is not disturbed for four days, which further aids in the fixation of the ileum to the abdominal wall. Irritation of the surrounding skin as a result of the discharge of ileal contents is easier to prevent than it is to correct once it has occurred. Consequently, the care of the skin begins with the application of compound tincture of benzoin at the time the initial dressing is applied and is repeated at each change of dressings thereafter. About the fifth or sixth postoperative day the catheter is removed, and the skin further protected by a sheet of rubber dam cemented to it, the ileostomy being brought out through a hole in the center. Skin irritation is a

problem only in the early period following the establishment of the ileostomy, for the Rutzen or similar type of bag eliminates the difficulty by preventing the ileal contents from coming in contact with the surrounding skin. The patient is carefully measured for this bag as soon as the ileostomy has shrunk to its permanent size and shape, which takes at least two months.

The maintenance of a normal electrolyte balance may become a serious problem during the early postoperative period. If even temporary obstruction occurs as a result of an adhesion, torsion of the ileal loop or edema at the abdominal wall, it is quickly followed by nausea and vomiting, and a loss of fluids and electrolytes, particularly chlorides. Dehydration, hypochloremia and acidosis may be produced by a hyperfunctioning ileostomy. Drowsiness, weakness and nausea suggest salt depletion and prompt measures should be taken to correct it.[10] The ileostomy fluid contains a large amount of sodium and potassium, and more fixed base than fixed acid. The sodium and potassium ions must be replaced. Sodium should be replaced as sodium bicarbonate, as well as sodium chloride, lest hyperchloremia be produced. Hartmann's solution, which contains sodium chloride, potassium chloride and racemic lactate (the last of which is metabolized to form glucose and bicarbonate), is particularly helpful in this situation. Occasionally, patients fail to improve and their chlorides remain low despite the administration of adequate amounts of sodium chloride. In these patients one should suspect a low serum potassium level. This can be checked by blood studies and by the typical changes in the electrocardiogram. If a low serum potassium is verified, administration of sodium chloride should be stopped, for more sodium will drive out more potassium and result in a further deterioration in the clinical condition of the patient. When the potassium level is brought back to normal with potassium chloride by mouth or by vein, the chloride level will also return to normal.

The patient mortality in all patients operated upon up to 1947 was 22.3 per cent. The mortality following ileostomy was 18 per cent. In many of these cases surgery was employed as a last resort, and some patients were already moribund when operated upon. As further experience was gained, patients who obviously were not responding satisfactorily to medical management were operated on earlier, and in the group of 97 operations during 1947 and 1948 the patient mortality was 4.1 per cent. The mortality for ileostomy alone was 5.6 per cent. The operative mortality was 2.6 per cent. Two of the 4 deaths followed ileostomy, and 2 followed ileostomy combined with right colectomy.

Not only can the lives of many patients with severe ulcerative colitis be saved by operation but also, with the aid of the modern ileostomy bag, these incapacitated, depressed persons can be restored to normal social and economic activity with a healthy, enthusiastic outlook toward life.[11] In the first group of 166 patients there were 3 suicides. There have been none since 1940.

Conclusion

Surgery has a definite place in the treatment of ulcerative colitis. If used when indicated as a complement to medical treatment, it will reduce the mortality and greatly reduce the morbidity associated with this disease.

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NEUROFIBROSARCOMA OF THE VAGUS NERVE*

Report of a Case

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NEUROGENIC tumors of the anterior mediastinum are comparatively rare. Kent et al.[1] collected a personal series of 21 neurogenic tumors of the mediastinum at the Barnes Hospital and reviewed 105 cases discovered in the literature. There were only 2 anterior neurogenic tumors in the series at the Barnes Hospital, and only 3 additional cases were found in the literature. The following case report is unusual because of the finding of a vagus-nerve tumor presenting both in the neck and in the anterior superior mediastinum.

CASE REPORT

S. L., a 51-year-old machinist and World War I veteran, was admitted to the hospital on February 21, 1949, complaining of a swelling in the right side of the neck. Five years previously he had first noted a swelling in the area that gradually increased to the size of a walnut and was sensitive to touch. The tumor fluctuated in size. When it was largest, the patient experienced extreme malaise and anorexia. Since the onset of the present illness he had noted a chronic cough and slight hoarseness. The tumor was found during a routine outpatient physical examination, and the patient was referred to the hospital for treatment. There had been no weight loss, dysphagia or regurgitation. The past and family histories were irrelevant.

Physical examination revealed a well developed, middle-aged man of average build who did not appear ill. On the right side of the neck just above the clavicle and behind the right sternocleidomastoid muscle origin there was a soft, slightly tender, movable mass, measuring 3 by 3 cm., that on forced expiration appeared to be pushed anteriorly and seemed larger. Pressure on the mass caused a severe spasm of nonproductive coughing. There was no increased retrosternal dullness. The heart and lungs were normal.

The blood pressure was 160/104; the pulse was 94, and the temperature 99.2°F.

Laboratory examination was completely negative. The basal metabolic rate was + 17 per cent. X-ray examination of the chest revealed a normal heart and lungs, but there was a swelling in the right superior mediastinum extending into the right hemithorax. Barium swallow and fluoroscopy of the chest showed displacement of the esophagus to the left. The mass moved upward when the patient forcibly expired against a closed glottis, but it did not move on swallowing. The trachea was displaced slightly to the left. The tumor was not calcified, but it was definitely lobulated.

Esophagoscopy, bronchoscopy and several laryngoscopies were within normal limits. It was believed that this mass was not connected with the thyroid gland, and a preoperative diagnosis of ectopic substernal thyroid tumor was made. On March 23 a transverse incision was made just above the right clavicle. The clavicular portion of the sternocleidomastoid was divided, and a firm grayish mass was exposed that was continuous proximally with the right vagus nerve within the carotid sheath. The mass entered the superior mediastinum posterior to the right innominate vein (Fig. 1). It was dumbbell in shape, and its larger portion appeared to be within the mediastinum. Consequently, parasternal portions of the clavicle and the first and second ribs were removed, and the pleura was opened. The intrathoracic portion of the tumor was found to be about 4 cm. in diameter. There was no doubt the tumor rose from the right vagus nerve, which was injected with novocain above the tumor. When this was done, the pulse rate rose from 90 to 120. The blood pressure and respirations remained the same. After the vagus nerve was sectioned proximal to the tumor, the pulse rate gradually returned to normal. The vagus nerve was also divided distal to the mass, but on attempts to remove the tumor it was found that a portion of it extended back underneath the subclavian artery along the course of the right recurrent laryngeal nerve. It was traced back up into the neck medial to the carotid artery and between it and the thyroid gland. When this portion had been removed, no tumor could be seen in the neck or within the anterior mediastinum. However, on palpation posteriorly more nodular tumor could be felt that appeared to extend behind the arch of the aorta and the base of the great vessels. It was impossible to ascertain how far the mass extended to the left. Because it was believed that the remainder of the tumor could not be approached through the anterior exposure, it was decided to discontinue the operation. The wound was closed in layers, and the patient was returned to the ward in good condition.

Pathological examination of the specimen by Dr. Raymond Yesner was reported as follows:

> The specimen consists of three fusiform pieces of red-white, soft pieces of tissue measuring 7 by 1.5 by 2 cm., 5 by 3 by 1 cm. and 2 by 1.5 by 1 cm. The three together weigh 25 gm. The largest is dark red, soft and somewhat cystic. It is sectioned longitudinally, disclosing several small cystic areas containing bloody fluid, embedded in firm, light-tan tissue, in strands and whorls, separated by fibrous trabeculae. The other pieces present essentially the same picture on section, except that the cavities are larger. Microscopical examination (Fig. 2) reveals findings compatible with a neurolemma but with disturbing features. No mitoses are noted. The completely atypical feature is the number of hemangiomatous foci, consisting of several cavernous channels, lined by endothelium and embedded in collagen. These vessels contain thrombi varying from very fresh to old and organized. In the capsule to the tumor are several myelinated nerves. The tumor is quite well encapsulated. The diagnosis is neurofibrosarcoma with hemangiomas.

The postoperative course was uneventful. The patient's voice was husky on recovery from anesthesia, and examination of the larynx showed paralysis of the right vocal cord. He has continued to be asymptomatic with the exception of hoarseness and occasional attacks of hiccuping. The spasms of coughing have disappeared, and he has resumed his normal occupation.

The location of the tumor and the fact that it did not move with the thyroid gland on swallowing might have suggested that it was actually within the carotid sheath. The fact that the patient had some hoarseness should have implicated the right recurrent laryngeal nerve although paralysis of the larynx was not demonstrable. This nerve also supplies sensory fibers to the lower larynx and trachea. It was probably the stimulation of these fibers that gave rise to the severe coughing spells

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on pressure over the tumor. Since the tumor arose from the right vagus nerve, it was necessary to remove a segment of the vagus nerve above and below the lesion. That the tumor was malignant was suspected when it was not possible to dissect it from the nerve trunk. This fact was borne out by the microscopical examination (Fig. 2).

Discussion

Among 25 peripheral-nerve tumors unassociated with von Recklinghausen's disease, Cutler and

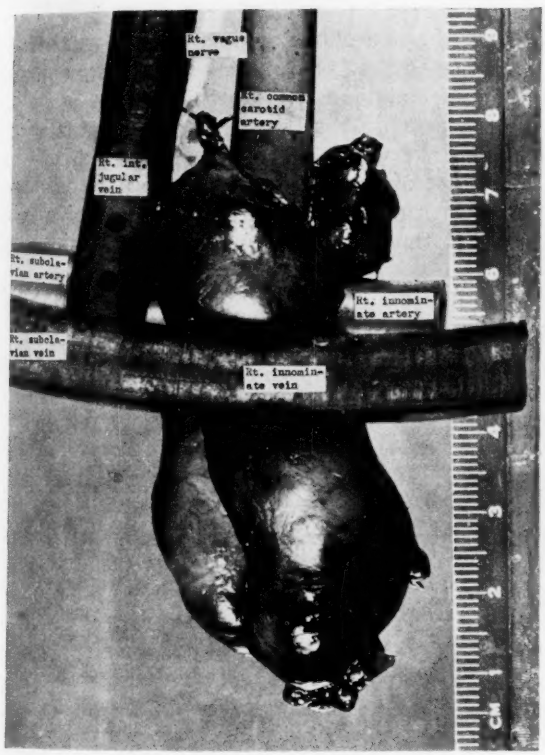

Figure 1. *Photograph of the Tumor Removed at Operation. An attempt has been made to represent the vessels by means of rubber tubing in order to demonstrate the relations of the tumor mass to the blood vessels at the base of the neck and in the superior mediastinum. The anterior vessels represent the innominate and jugular veins.*

Gross[2] reported 2 of vagus-nerve origin. The symptoms in 1 patient were hoarseness and coughing. A cervical mass was resected together with the left vagus nerve, and the patient was asymptomatic for five years, when he died of pneumonia. A second patient complained of hoarseness and a large cystic mass in the neck. This tumor was resected, the left vagus nerve being left intact. The patient was asymptomatic five years later.

In 1943 Blades and Dugan[3] reported a successful resection of a primary tumor of the vagus nerve in the thorax of a patient with von Recklinghausen's disease. At operation a ganglioneuroma of the posterior mediastinum was found. This was divided into two parts, one of which originated from the upper dorsal sympathetic chain and the other from the left vagus. Furrer and Fox[4] described a

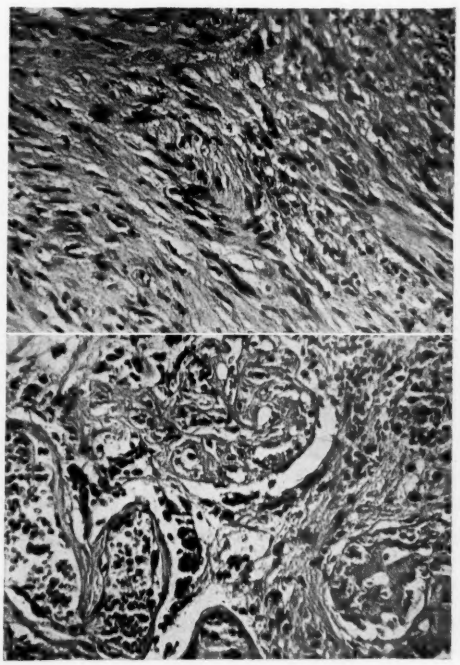

Figure 2. *Photomicrograph of a Section of the Tumor. Microscopical examination revealed rather poorly developed Verocay bodies in the periphery and areas of loose, myxomatoid structure of the Antoni type in the center, the nuclei varying in size and shape from elongated in the Verocay portion to cells of two or more nuclei with prominent nucleoli in the Antoni part* (A). *The completely atypical feature is the number of hemangiomatous foci* (B) *consisting of several cavernous channels, lined by endothelium and embedded in collagen. (Diagnosis: neurofibrosarcoma with hemangiomas.)*

perineural fibrosarcoma of the left vagus nerve that was found at autopsy. This patient had been subjected to two subtotal thyroidectomies for hoarseness three years prior to his death. At autopsy the fibrosarcoma was metastasized to the tail of the pancreas. The tumor extended from the left mastoid region to the supraclavicular area and did not invade the mediastinum. Bustos[5] reported the successful extirpation of a tumor of the right vagus nerve that extended from the angle of the jaw to the level of the cricoid cartilage. He stressed the symptom of coughing on compression of the tumor and noted the elevation of the pulse rate following removal of the lesion. Paralysis of the right vocal cord was present some months after operation. The most detailed discussion of vagus-nerve tumors

appeared in a presentation of a case of von Recklinghausen's disease by Bruckschwaiger.[6] Multiple neurofibromas had been removed. The presenting complaints were coughing on compression of a mass in the neck and hoarseness. The patient also noted that he had had epigastric cramps of recent origin, particularly when he was wearing a tight collar. At operation the tumor was resected, and the vagus nerve left intact. Four weeks after operation the hoarseness and epigastric distress had disappeared. An interesting feature of this case was the epigastric pain, which may be attributed to vagal overactivity due to compression by the tumor.

Changes in cardiac rhythm following section of only one vagus nerve are rare. In the case reported above, there was only a transitory rise in the pulse rate after the division of the vagus nerve. However, the patient reported by Bustos[5] had persistent tachycardia although the rate appeared to be reverting to normal several months after operation. Section of the vagus nerve above the pulmonary hilus has frequently been performed during total pneumonectomy or resection of the thoracic esophagus without serious sequelae. There is convincing clinical evidence, therefore, that interruption of a single vagus nerve in the human being is of little consequence. There is, however, 1 case[6] in which cardiac standstill occurred just after the interruption of a vagus nerve. Infiltration of the nerve with a local anesthetic prior to division seems indicated.

It is widely known that a high incidence of malignant degeneration is associated with primary neoplasms of the peripheral nerves. Kent et al.[1] found an incidence of 41 per cent in mediastinal neurogenic tumors seen at the Barnes Hospital and 37 per cent in the 105 cases that they collected from the literature. In the case reported by Bruckschwaiger[6] malignant recurrent neural tumors of the brachial plexus eventually developed. The incidence of malignant lesions in tumors of the peripheral nerves and in tumors of the mediastinum is sufficiently high to warrant as radical an excision as possible, even if the operation entails the sacrifice of a vagus nerve. Unfortunately, this was not possible in the case reported above, because of the inaccessibility of the retroaortic portion of the tumor at operation.

Summary

A case of a neurofibrosarcoma of the vagus nerve located in the base of the neck and in the anterosuperior mediastinum is presented.

The symptoms that are likely to appear with tumors of the vagus nerve are discussed.

The onset of coughing or epigastric pain on compression of a mass in the neck is presumptive evidence that the tumor is of vagus-nerve origin.

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MEDICAL PROGRESS

ECZEMA IN INFANCY AND CHILDHOOD (Concluded)*

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TREATMENT OF SECONDARY INFECTION

Secondary infection of the skin in eczematous infants and children is common, and treatment is very satisfactory when carried out correctly.

Pillsbury,[28] in a comprehensive paper, discusses the management of bacterial infections of the skin. Bacteria rapidly gain a foothold in skin that is already diseased, and the problem of their removal is complicated by the fact that such skin reacts more adversely to treatment than skin that was previously normal. It should be especially borne in mind that in chronic eczematous lesions in which infection plays a part in keeping the process active there may be no gross evidence of infection, such as pustulation—the skin may present simply an eczematous appearance. From the normal skin, staphylococci are often recovered by culture, although coagulase-positive hemolytic *Staphylococcus aureus* is found more frequently on the frankly infected or eczematous skin. Beta-hemolytic streptococci are not commonly found on normal skin. The bacteria of the skin are almost always of some importance in the etiology of eczema, and may keep it active by acting as skin sensitizers.

Penicillin in ointment form is efficient in the treatment of most pyodermas: sensitization, however, is not uncommon. Penicillin by injection is more efficient, and there are fewer sensitivity reactions. Local sulfonamide therapy of superficial skin infections is rarely justifiable — sensitization is far too frequent. The use of ammoniated-mercury ointment in excess of 5 per cent strength is rarely necessary. Acriflavine compresses in 0.01 per cent strength are often very effective for infected, oozing areas. Castellani's carbol fuchsin paint in chronic low-grade eczematoid infection is excellent. Silver nitrate, in compresses of 0.10 per cent strength or painted on in 1 per cent strength, is also a very good remedy, and will cause no untoward reactions if not used in greater concentration than this.

The use of chemical irritants or of highly sensitizing compounds on infected, inflamed skin will result in severe reactions. In particular, tincture of iodine should never be used.

Gottschalk and his associates,[29] after an extensive use of penicillin ointment in the treatment of impetigo and secondary skin infections, came to the conclusion that the local application of penicillin does not give better results than the older antiseptics, and that since the percentage of reactions to penicillin ointment is rather high, this drug may prove to be less useful in the treatment of skin infections than some of the older antiseptics.

Conservative dermatologic opinion is well expressed as follows by Epstein[30]:

> In spite of difference of opinion regarding the efficiency of topical penicillin, it is safe to state that this method did not bring about any great revolution in therapeutics. In a given case, topical penicillin may work better than other antiseptics, but in general, penicillin ointments or creams are not superior to other antiseptics used for local application. The great value of penicillin therapy depends entirely on parenteral administration. There are numerous reports of sensitization to penicillin from local application. In view of these facts penicillin should not be used externally in otherwise harmless skin conditions except when really indicated.

BACITRACIN

Bacitracin is a newer antibiotic derived from a strain of *Bacillus subtilis*. It is active against gram-positive bacteria.

Eichenlaub and Olivo[31] treated 50 patients who had pyogenic dermatoses with an ointment containing 500 units per gram of bacitracin, in a water-miscible base. Forty-four patients were improved or cured in one or two weeks. The results in impetigo and ecthyma were brilliant. A contact type of sensitization dermatitis due to bacitracin developed in 2 patients.

Miller, Slatkin and Johnson[32] treated patients who had pyogenic dermatoses with bacitracin ointment. In 18 patients with impetigo the median time for cure was eight days. Of 16 patients with folliculitis and sycosis vulgaris, 5 were cured; in 6 the infection was "controlled," and there were 5 failures. In 13 cases of infectious eczematoid dermatitis, 10 of 11 patients adequately followed were cured in a median time of ten days; 1 case was a failure. In 10 cases of vesicopustular eruption of the hands 4 of 7 patients adequately followed were cured in a median time of fourteen days; 2 cases were improved, and 1 was a failure. Five cases of ecthyma were cured in a median time of fourteen days. The authors are of the opinion that bacitracin compares favorably with penicillin in effectiveness and has the advantage that there is a very low sensitization

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rate. They stress the desirability of using it in a water-soluble base.

Derzavis, Rice and Leland[33] treated 138 cases of pyogenic disease of the skin with bacitracin ointment. Therapeutic response was excellent in most cases, and the authors conclude that bacitracin is a potent agent for the treatment of superficial pyodermas.

For secondarily infected eczema in infants and children, penicillin by mouth, 100,000 units three times a day, is excellent, and it is no exaggeration to say that for diffusely scattered infection, in which local treatment is somewhat difficult, penicillin by mouth or by parenteral administration has completely revolutionized the treatment of this troublesome and common complication of infantile eczema. For local treatment I prefer 3 per cent ammoniated-mercury ointment for the glabrous skin, and 5 per cent for the scalp; for oozing areas of fairly large extent, one fourth of 1 per cent silver nitrate solution sopped on frequently, and for small oozy pustules, Wyeth's Alulotion (colloidal ammoniated mercury) are effective. In the treatment of a large number of infants and children with secondarily infected eczema, I have seen only 2 who were sensitive to mercury. It is furthermore a very simple matter to do a patch test with mercury ointment before one employs it in actual treatment. If local treatment is to be used over a very large area, penicillin ointment is probably better than ammoniated mercury, on account of the possible danger of mercury absorption.

Fungi

Perlman[34] tested 68 eczematous infants and children with five different fungous extracts (including Oidiomycin and trichophytin) — 0.10 cc. intracutaneously, for reactions delayed for twenty-four hours, similar to the tuberculin test.

There were no positive reactions. Scrapings and cultures were made and examined for fungi; no pathogens were found. Perlman concluded that fungous infections of the skin played little part in the eczematoid dermatoses of infants and children. This was a very careful and accurate piece of work, and the conclusions are justified by the evidence. It must be remembered, however, that moniliasis of the skin *does* occur in infants and children, and that it may be mistaken for atopic dermatitis by those who are not expert dermatologists.

Scabies

Scabies is not uncommon in infants, and is frequently mistaken for eczema and treated as such. The skin of a baby is tender, and secondary dermatitis has been common with the older standard methods of treatment. The reports of Wooldridge[35] and of Cannon and McCrae[36] on the use of a new and entirely nonirritating scabicide are of considerable interest. Wooldridge treated 72 patients with the gamma isomer of hexachlorocyclohexane* in the form of a 1 per cent ointment in a vanishing-cream base. Of the 72 patients, 69 were cured with a single application. Three patients had relapses, and of these 1 was cured with a second application of the ointment, whereas the 2 others were treated with benzyl benzoate, because the supply of Kwell was temporarily exhausted. No irritation was noted in any patient. The authors conclude that this drug is better than any other for the treatment of scabies. Cannon and McCrae treated 100 patients. All were cured with from one to three applications, no irritation was noted, and there was no sensitivity, either primary or secondary, to the drug or the vehicle. Without preliminary bathing, a thin film of the cream was rubbed into the entire cutaneous surface of infants and children, and from the neck to the soles of the feet in adults. A bath was taken at the end of twenty-four hours, and the bed linen and underwear changed and boiled. Patients were observed weekly, and if there were any signs of activity the treatment was repeated. Two thirds of the patients treated showed no signs of activity after one treatment. Thirty-six were given two treatments, and 3 patients received three. All were cured. This seems to be a real advance, particularly for infants and children. I have had opportunity to use this treatment in a few cases, with excellent results in all.

Kaposi's Varicelliform Eruption and Eczema Vaccinatum

In 1887 Kaposi[37] first described this eruption, as follows:

> A very alarming complication of eczema infantum which has come under my observation is an acute outbreak of numerous vesicles, partly scattered, partly arranged in groups. The vesicles are as large as a lentil, filled with clear serum, and the majority are umbilicated. They look like varicella lesions. There is an associated high temperature. The vesicles develop very rapidly in large numbers, and often continue to appear in successive crops for as long as a week. The largest number of these varicella-like lesions are found upon the already eczematous skin, but smaller groups may appear upon the previously intact skin.

It has recently been proved by several investigators that this eruption is due to the virus of herpes.[38-40] The appearance of Kaposi's eruption is very similar to that of eczema vaccinatum, which is not uncommon and which is likely to appear in eczematous infants and children if they are exposed to a sibling a short time after he has been vaccinated. By virus studies it can be shown, however, that Kaposi's eruption is due to the virus of herpes, and eczema vaccinatum to that of cowpox. Riley and Calloway[41] are of the opinion that although these two conditions present very similar clinical characteristics, a differentiation can usually

*Marketed as Kwell ointment by the Commercial Solvents Corporation, New York City.

be made on clinical grounds, without virus studies, for in eczema vaccinatum there is usually a history of vaccinia contact, and the lesions go through the usual course of a vaccinia eruption. They also have a tendency to coalesce and form large, bullous lesions. The vesicles in Kaposi's eruption are often herpetic, and the grouping of the lesions, characteristic of herpes simplex, is striking.

Fries, Borne and Barnes[42] report 16 cases of eczema vaccinatum occurring in eczematous children during a mass vaccination campaign in New York City. Each child had been exposed to a recently vaccinated person. The incubation period averaged ten days. The eruption was essentially pustular — some lesions were almost bullous in size. There was cellulitis of the face and edema of the eyes, and marked lymph-node enlargement. By the second week of hospitalization the lesions were healed, leaving small depigmented scars. Alopecia, which was a striking complication, occurred in 10 patients. This was total in several patients, but there was a complete regrowth of hair in about four months.

Penicillin was given parenterally to all patients, and local treatment consisted of wet compresses of 1:20 Burow's solution.

In another paper, Fries and Borne[43] reported virus studies in 9 of the patients previously discussed, and all showed definite evidence of vaccinial antibodies. Fifteen patients were vaccinated during convalescence; all reacted with an immune response.

Fries and Borne are of the opinion that both eczema vaccinatum and similar eruptions caused by the herpes virus should be called "Kaposi's varicelliform eruption," in spite of the fact that each is caused by a different virus, and that they also present certain clinical differences.

Aureomycin Therapy

Inasmuch as aureomycin is effective against some viruses, one would expect that it might be of value in the treatment of "Kaposi's varicelliform eruption" and "eczema vaccinatum." Perry and Martineau[44] report its use in a severe case of eczema vaccinatum. The patient was a one-year-old eczematous child who contracted eczema vaccinatum from a playmate who had been recently vaccinated. The child was treated for two days with penicillin, which accomplished little. On the third day aureomycin was started (250 mg. every six hours). Within twenty-four hours recession and drying of the vesicles was noted, and the temperature, which had been 104.8°F., began to fall rapidly. It was normal in seventy-two hours, and the child's general condition was much improved. The child was discharged well on the eleventh hospital day.

Nummular Eczema

Nummular eczema (Van Studdiford, McLean and Alvarado[45]) is characterized by circumscribed patches, which in the beginning are dry but which often become edematous and later may become lichenified. Each patch consists of innumerable small vesicles, the patches varying from the size of a ten-cent piece to that of a dollar bill. The sites of predilection are the extensor surfaces of the extremities, but patches may occur anywhere. Itching is intense. The authors report good therapeutic results with the daily intravenous injection of 50 mg. of pyridoxine hydrochloride (adults). For local treatment they used compresses of boric acid solution and starch, followed by calamine liniment or zinc oxide paste. Engman, in discussion, said that very little is known of nummular eczema, except its clinical appearance. It usually begins in the fall and lasts until spring, and is very resistant to treatment. The etiology is entirely obscure. Engman has had best results with the intravenous injection of arsenic in the form of iron cacodylate. A few particularly resistant cases have cleared in a hot, dry climate. Local treatment gives hardly any result. Robinson, in discussion, said that he had used pyridoxine without any results. Austin, in discussion, recommended liver injections and the administration of various components of the vitamin B complex.

It is apparent, from the numerous methods of entirely empiric treatment recommended for this condition by various authors, that none is much good. Nummular eczema is not very uncommon in infants one to two years of age. It probably has nothing to do with allergy, but by those who are not familiar with it is usually mistaken for atopic dermatitis. I have had fair therapeutic results by painting each lesion with crude coal tar once a day. No change in diet is indicated. Nummular eczema is not mentioned in many dermatologic textbooks. The best discussion of it anywhere is given by Sulzberger and Wolf.[46]

Seasonal Eczema Due to Pollen

Seasonal eczema due to pollen is not uncommon in children. It may be due to external contact with the oily fraction of the pollen grains, or to the water-soluble fraction, which probably reaches the sensitized skin by inhalation. In the first situation positive patch tests are obtained with an extract of the oily fraction, and in the second positive scratch or intracutaneous tests are obtained with the water-soluble fraction. It is generally thought that the first type of dermatitis (contact) is uncommon in children, and that it occurs especially in farmers and other outdoor workers who are continually exposed to a very high pollen concentration, particularly in the Middle West. Contact with the leaves of the plant ragweed may also produce this type of dermatitis in susceptible persons. It is probably not nearly so common in New England as the second type of pollen dermatitis, which is generally believed to be due to inhalation of the pollen,

and in this area there is sensitization to the water-soluble pollen fraction. This is true atopic dermatitis, and while its occurrence has been for some time recognized by allergists and dermatologists, few systematic studies have been reported, with the exception of papers by Feinberg[47] in 1939 and by Mitchell and Mitchell[48] in 1945. Rowe's[49] very comprehensive paper is therefore of considerable importance. He reports 16 cases of atopic dermatitis of the hands due to pollen. He believes it is due to the water-soluble pollen fraction and that this gains access to the skin by inhalation. The history is very important, and if the dermatitis is strictly seasonal and recurs at the same time each summer, pollen dermatitis should be suspected. Scratch tests with pollens may be positive or negative. If the history is characteristic, negative tests do not rule out pollen as a cause. Treatment is by hyposensitization with a mixed extract containing all the pollens to which the patient is exposed during the period in which the dermatitis is active.

The most startling thing about Rowe's treatment is the extraordinarily small doses of pollen extract used. Treatment is begun with 0.10 cc. of a dilution varying from 1:5,000,000 to 1:5,000,000,000. Injections are given every one to three days, and inasmuch as with these high dilutions there is no danger of a constitutional reaction, they may be given by the patient. If there is increased itching or any flare-up of the dermatitis after an inoculation, the dose has been excessive, no matter how small it was. When pollen leaves the air stronger solutions of the antigen may be tolerated, even up to a 1:50 dilution, and by the next season, when pollen returns to the air, hyposensitization may have been attained, so that much stronger dilutions may be tolerated than were tolerated the first summer, but as a rule a marked reduction of dosage during the pollen season is necessary.

Rowe has obtained excellent results with the perennial injections of dilutions no stronger than 1:5,000,000,000. Inoculations need to be continued for several years, as in hay fever. He reports 6 cases in detail, treated by hyposensitization. Excellent therapeutic results were obtained in all.

In my opinion this is one of the most important contributions of recent years to the therapy of atopic dermatitis. The diagnosis of pollen dermatitis is easy; the treatment is difficult, because there is no possible way of preventing it unless hyposensitization is attempted. It is, however, always a question whether to do this or not, because there is so much likelihood of making the dermatitis worse if the tolerance is exceeded, and the tolerance is often small. Although Rowe's dosage may seem absurdly small, it was well recognized by Walker[50] in 1918, when he was the first to discuss hyposensitization to environmental allergens in atopic dermatitis, that these patients can by no means tolerate the dosage of pollen that is given in hay fever, and it may be that those who have found hyposensitization with environmental allergens in atopic dermatitis of no value (and they are many) have arrived at this conclusion because too large doses were used. I have seen a severe flare-up produced by the inoculation of 0.05 cc. of a 1:1,000,000 dilution of a mixed pollen extract in a child with seasonal atopic dermatitis due to pollen.

According to Tuft,[51] not enough attention has been paid to inhalant allergens as causes of atopic dermatitis. With this, I heartily agree — in older children and adults the allergens are far more important than foods. House dust is particularly important. Of 54 patients with atopic dermatitis tested by Tuft with house dust, all showed positive reactions, and 7 had noted definite aggravation of symptoms from exposure to dust. Tuft believes that it probably works by inhalation rather than by contact. Appreciation of the possible role of pollen sensitivity is also essential to the proper management of many patients with atopic dermatitis. Tuft reports successful hyposensitization in 2 patients with atopic dermatitis due to house dust.

When one is dealing with chronic atopic dermatitis that has persisted for some years, a history of seasonal aggravation is of the utmost importance, since it gives a clue to the cause. In the summer this is often pollens and molds, and in the winter house dust or wool.

Blood Protein Depletion

Although it has been known for a long time that in some infants with generalized dermatitis (atopic erythroderma, Leiner's disease) edema may develop on account of a low serum protein, Wolpe[52] is the first systematically to study this and to place special emphasis upon it. He found that 26 of 54 cases of infantile eczema showed a low serum protein, which caused "nutritional crises." These are manifested by a sudden gain or loss in weight (edema or dehydration), apathy, anorexia, diarrhea or acute prostration. Wolpe's treatment is as follows:

Liver extract intramuscularly twice a week: for infants under six months of age 0.5 cc. (7.5 units), and for infants over six months of age 1 cc.

Vitamin B complex, 1 cc. intramuscularly twice a week.

Intravenous administration of plasma once a week when the total blood protein value falls into the range of 5.5 to 6.0 gm. per 100 cc., and twice a week when it is below 5.5 gm. Blood is alternated with plasma when the hemoglobin value is low.

One tablespoonful a day, by mouth, of a hydrolyzed amino acid mixture.

This is an important paper. If there is extensive scaling, as there usually is, in what I have called

"atopic erythroderma," a large amount of nitrogen may be lost from the body. Or if there is much oozing, the same thing may occur. These children not only have dermatitis but also may be seriously ill, and proper treatment of their metabolic derangement is often more important than treatment of the skin.

Hospital Morbidity of Eczematous Infants

It is well known that infants with eczema are unduly susceptible to infection, and for that reason it has been advocated by some that they should not be hospitalized, for cross-infections on most infants' wards are common.

Schwartzman,[53] in a comparison of a series of hospitalized infants who had eczema with a series of normal infants and some with other diseases, found that upper respiratory infections were acquired nearly twice as often by the eczematous infants as by the others.

Whether or not an eczematous infant should be hospitalized is often a difficult question to decide. The dictum that such infants should never be hospitalized cannot be accepted as a universal rule, although there are some undoubted disadvantages to hospitalization, not the least of which is the fact that if any benefit is to accrue from hospitalization, the infant must be kept in the hospital for at least several weeks, and in these days this is very expensive. I do not recommend hospitalization for any eczematous infant unless the eczema is very severe, or complicated by other trouble, and therapeutic procedures are necessary that cannot be done well at home, or unless the mother is so worn out with the constant care of her fretful, continually itching child, and her many other household duties, that she needs a rest. This is often the most important practical reason for hospitalization and, in my opinion, a good one — twenty-four hours a day with an eczematous infant is no picnic.

Summary

In the last four years little progress has been made in the study and treatment of eczema in infants and children. It is still treated much as it has been for the last twenty years — no spectacular cure is at hand. The antihistaminic drugs have not contributed much, and unsaturated fatty acid therapy has not yet become standard.

There has, however, been a greatly increased interest in this disorder, and most of those who are particularly concerned with it write profusely, so that there has been a considerably greater dissemination of what facts are known, which has probably brought about generally better treatment.

Original investigations that have added to existing knowledge have been few. Rowe's studies on pollen dermatitis, Wolpe's observations on low serum protein and the work that has been done by several individuals and "teams" on Kaposi's varicelliform eruption represent about the only new and original contributions. To quote R. A. Cooke[54] "Allergic dermatitis is today, I think, the number one problem child of allergy. What is needed is more light and a new approach."

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 36091

PRESENTATION OF CASE

A forty-two-year-old man entered the hospital for neurologic study.

He had always been well until seven months before admission, when, while at a summer camp with many of his fellow-workers, he awakened everyone early one morning because he had the delusion that there was a burglar about; a little later he accused one of his superiors of harboring the burglar. It was recognized that he was ill, and he returned home. He remained away from work for three months and apparently recovered. About one and a half months before admission, he began to be confused, asking the same question repeatedly within a few minutes, and answering irrelevantly when asked a question. At about this time, his speech began to be slightly slurred. He had no difficulty with the use of his limbs. Three weeks before admission, he suddenly felt ill, vomited and began to stagger on walking. His speech was extremely slurred, but he had no apparent difficulty in understanding what was said to him. He complained of a mild unlocalized headache. During the following day, his condition improved somewhat, but a day later he had a sudden sensation "as if struck in the mid-forehead," after which his arms and legs trembled vigorously for about thirty minutes. He did not lose consciousness, and was able to walk with assistance and to speak. When he tried to get up the next morning, his gait was extremely unsteady, and there was a gross tremor of his arms and legs. For several hours he coughed back whatever liquids he attempted to swallow. During the course of that day, there was a brief episode of unresponsiveness, in which his "eyes rolled in his head," followed by diplopia. On the next day, his gait improved, but that evening the head was suddenly thrown back and there were jerking movements of all four limbs, which were held rigidly in extension. The eyelids were closed, and the jaw was tightly clenched. There was no incontinence or tongue biting. During the attack, the patient was able to indicate by gestures with the right hand that he could hear but could not speak. The extension and jerking of the limbs subsided in about thirty minutes, and speech returned although it was markedly slurred. The patient was then admitted to another hospital, where he stayed for about ten days, during which his condition steadily improved. It was first noticed during this time that the right side of his mouth was drawn up very slightly as compared with the left when he talked. On his return home, one week before his admission to this hospital, he obviously was not well, his speech was slightly slurred, and he said that his left arm and leg felt weak. Three days before admission, he had another attack of rigid extension of the limbs, with a fine, rapid tremor of the legs and right arm, lasting several hours. During the attack he was unresponsive and afterward did not speak again or move his limbs. He was readmitted to the other hospital and later transferred here. Throughout this illness, he had had no pain, and only occasional headache, which was never severe or localized. Except for transient diplopia following one of the convulsive attacks there were no visual symptoms.

The past and the family histories were noncontributory. The patient had never had a head injury.

On physical examination he was slightly cyanotic and appeared acutely ill. There were coarse rhonchi throughout both lung fields. The heart and abdomen were not remarkable. He made no spontaneous movements of the limbs, and he did not speak or obey commands. In response to painful stimuli, both sides of the face moved sluggishly and equally, and there was some movement of each limb. The fundi were normal. The pupils were equal, 1 mm. in diameter, and responded sluggishly to light. There appeared to be paralysis of abduction of the left eye and defective conjugate deviation of the eyes to the right. The tendon reflexes were a little more active on the left. Abdominal and cremasteric reflexes were absent; plantar reflexes were bilaterally extensor.

The temperature was 102.4°F., the pulse 100, and the respirations 30. The blood pressure was 130 systolic, 98 diastolic.

The urine was not remarkable. The white-cell count was 13,700, with 84 per cent neutrophils, and the hemoglobin 14.4 gm. per 100 cc. The spinal fluid was under a pressure equivalent to 130 mm. of water and contained 3 lymphocytes per cubic millimeter; the protein was 54 mg. per 100 cc., the chloride 129 milliequiv. per liter, and the gold-sol curve 0000000000. An electroencephalogram showed unsustained slight reduction in voltages and alpha

activity in the region anterior to the right occiput. Films of the skull and chest were normal.

An operation was performed on the evening of admission.

Differential Diagnosis

Dr. Jost J. Michelsen*: When I read this report last night — and I just got it yesterday — I felt rather strongly that the pathological findings obtained at autopsy should have been included in this summary. It seemed to me that an attempt to correlate the anatomical and clinical findings would give us many opportunities for interesting discussion. Some of the clinical manifestations that this patient showed would still be difficult to account for, such as the hallucination at the onset of the illness, the myosis of the pupils in the presence of oculomotor-nerve weakness on the right, the tremor and the confusion. Another immediate reaction was that the operation performed on the evening of admission was very probably only a minor one, perhaps an air study to rule out an expanding lesion. I just could not imagine that the clinical manifestations were produced by a lesion that would lend itself to a surgical approach.

Most of the signs described call attention to the brain stem. For instance, we have a classic description here of a "tonic" fit. We are told that the patient threw his head back — we call that opisthotonos — and there were jerking movements of all four limbs, which were held rigid in extension. The abstracter added generously that there was no incontinence, tongue biting or unconsciousness, all of which, if present during a seizure, would call for a diagnosis of epilepsy. Tonic fits are usually due to lesions at the level of the upper part of the midbrain. Most frequently, they are seen in cases of expanding lesions above the tentorium, producing herniation of the temporal lobe into the incisura of the tentorium and thus causing acute compression of the mesencephalon. There is nothing in the record to indicate that this patient had increased intracranial pressure as a cause of such a herniation, which is also observed in expanding lesions below the tentorium, probably as a result of embarrassment of the circulation of the midbrain. Needless to say, primary disease of the blood vessels could lead to this manifestation.

Another rather important sign suggestive of brain-stem involvement is the myosis of the pupils, which was present bilaterally on admission to this hospital. These small pupils reacted sluggishly to light. This observation precludes Argyll-Robertson pupils. Myosis with sluggish reaction to light is fairly often observed in cases of meningitis and subarachnoid hemorrhage. It occurs with pontine hemorrhage. The site of the involvement is dependent upon the general symptomatology. Its occurrence in thrombosis of the posteroinferior cerebellar artery is well known. I may add that the pin-point pupils in this case are of grave prognostic importance. I would not hesitate to predict that the patient died soon after his admission to the hospital, not as result of the surgery performed but from his disease.

The myosis of the pupils, of course, also is against herniation of the inner surface of the temporal lobe into the tentorial opening. Tentorial herniation produces compression of the oculomotor nerve, unilateral or bilateral, with dilatation of the pupil.

There are numerous other neurologic signs that permit us to place the lesion or, should I say more cautiously, the principal lesion in the brain stem. The patient had shown disturbances of articulation. His speech was slurred. In other words, his sound production was faulty. He did not speak or obey commands during the last stage of his illness, but during the course of his disease he apparently comprehended what was said to him and he was able to form words, until he was moribund, except for two occasions immediately after his mesencephalic seizures. It is said that when the slurring of his speech began, he had no complaints and no difficulties with the use of his legs. I do not know how much significance I should attach to this statement. We have to decide whether or not the weakness of the muscles of articulation was due to a lesion of the nuclei in the medulla oblongata or should be classified as a pseudobulbar palsy and bilateral pyramidal-tract dysfunction. The presence of bilateral Babinski reflexes on examination in the hospital and the absence of muscle wasting are in favor of the latter. The same considerations apply to the temporary disturbance of swallowing, which occurred about three weeks before admission.

The neurologic picture during the last stage of his illness also fits very well into our present conception of a brain-stem lesion. It is reasonable to assume that the patient had bilateral weakness of the face and extremities, bilateral abducens paralysis and weakness of the oculomotor nerve on the right. Abdominal and cremasteric reflexes were absent, and there were bilateral Babinski reflexes.

Now we come to some manifestations that I find very difficult to discuss. One of them is the tremor, which is described as a gross tremor of the arms and legs when he tried to get up one morning. I think that this is consistent with brain-stem involvement and perhaps signifies disease of the brachia conjunctiva. I wish Dr. Kubik would comment on the brief episode of unresponsiveness in which the eyes "rolled in his head." Certainly, Dr. Kubik will have the final word about the onset of the patient's illness. I realize that the elaborate visual hallucinations, which this patient had seven months before admission, are hardly consistent with brain-stem disease. It would be helpful to have some information about the patient's visual fields, but, of course, he was too uncooperative on

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admission for any field defects to be detected. I am wondering if perhaps the hallucinations came from the occipitotemporal region, possibly some lesion near area 19. The confusion about one and a half months before admission is also suggestive of an illness that was more diffuse and not limited

taken after introduction of air by burr holes show fair filling of the ventricular system. It is, if anything, very slightly wider than usual but reveals no gross distortion or displacement; the fourth ventricle and aqueduct are difficult to identify, but I think they can be seen in the film taken with the occiput

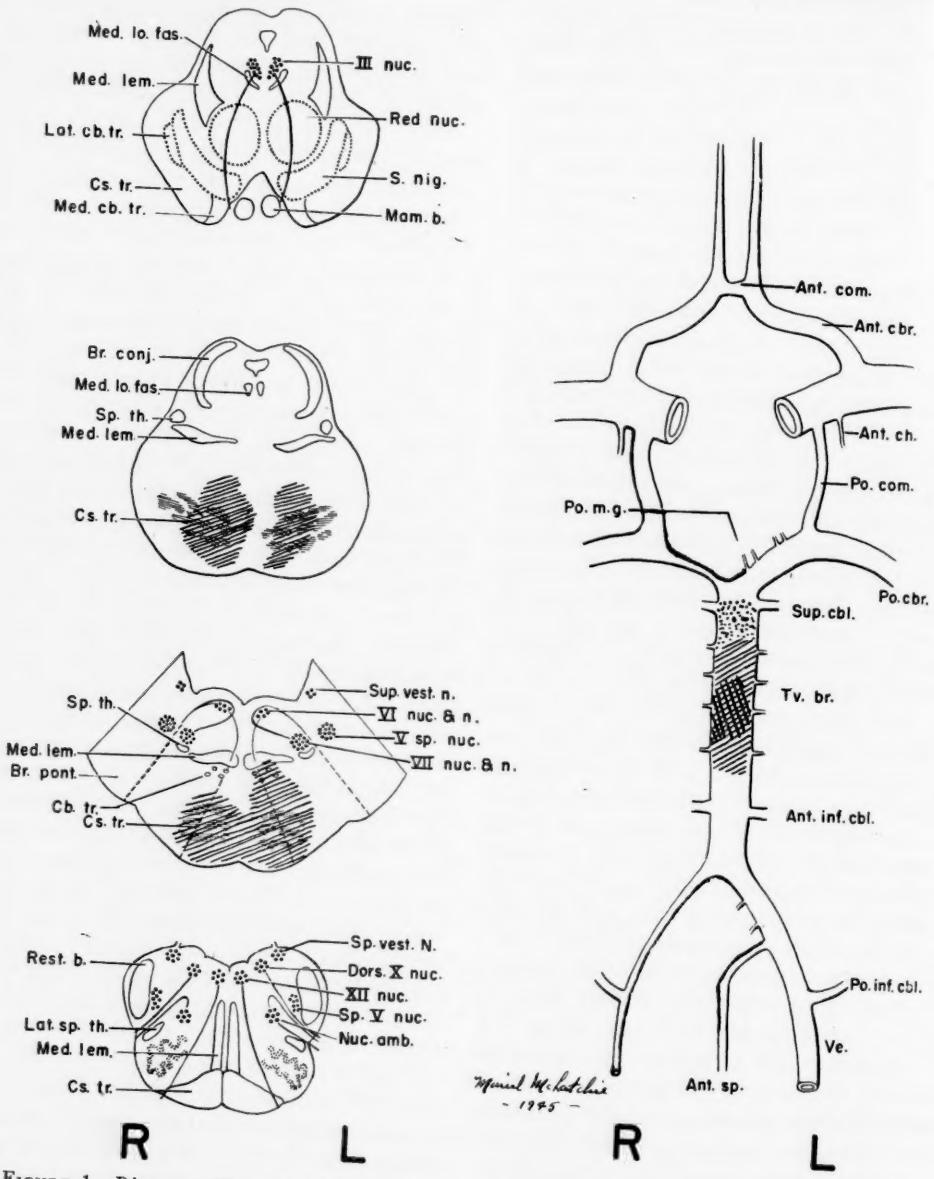

FIGURE 1. *Diagrams Illustrating Thrombosis of the Basilar Artery and Resulting in Infarction of the Pons.*

to the brain stem. May we perhaps at this point look at the x-ray films?

DR. STANLEY M. WYMAN: We have a ventriculogram.

DR. MICHELSEN: That is good.

DR. WYMAN: As the record states, the plain film of the skull shows no evidence of localized intrinsic bone disease, and there is no gross evidence of chronic increased intracranial pressure. The films

elevated, and there is definite air filling the basal cistern and descending down the brain stem.

DR. MICHELSEN: Is there anything about the pineal body that you might tell us?

DR. WYMAN: It is not calcified. On the plain film it cannot be identified, and, as far as one can say from these somewhat imperfect films, I can see no evidence of gross disease in or about the region of the pineal body.

DR. MICHELSEN: These ventriculograms are, of course, very much against a tumor, but let us continue with our discussion, using the clinical data, without paying too much attention to the accessory tests, including also the electroencephalogram, which does not help us very much in this case.

What type of lesion did this patient have? Did he harbor a growth or multiple tumors? Did he have vascular disease? Did he have an infection? Could this have been some form of degenerative disease?

One can be reasonably certain that he did not have an intracranial infection. There was no pleocytosis in the cerebrospinal fluid. The chloride was normal. The sugar is not mentioned, but probably was normal.

Discarding the possibility of an infection, we still have a rather generous choice. I do not know exactly how to make it. Obviously, this patient had remissions. Remissions are characteristic features in only one disease, and that is multiple sclerosis. The variations of the clinical manifestations in this case were considerable. Theoretically, there is a remote chance that this patient suffered from multiple sclerosis. However, the very short duration of the first manifestations, which very probably were part of the whole syndrome, is very much against it. Perhaps I am wrong in emphasizing the remissions in this case. The report does not make the course of events too clear, particularly the developments during the last six weeks of his illness.

I do not know of any other degenerative disease to be considered, and we now have to attempt a differential diagnosis between vascular disease and tumor. The intracranial pressure and fundi were normal. Normal pressure and fundi are occasionally seen in brain tumors, particularly in brain-stem lesions. The patient had only very little headache, which also does not rule out a brain tumor. Remissions in brain tumors are occasionally observed.

However, I am impressed by the sudden onset of what one might call the third episode three weeks before admission, when he suddenly felt ill, staggered and a day later had a sudden sensation as if struck in the midforehead. This sounds very much like vascular disease, probably not primary hemorrhage, but very possibly thrombosis or embolism. In this exercise one also should think of some of the very rare lesions. I just mention hemangioma in passing, although I have no evidence even to mention it briefly. The patient's heart was normal, and thus we might exclude embolism. The only alternative that remains then is thrombosis, which, if we consider the clinical signs, might well have taken place in the basilar artery. The patient was in coma. He had quadriparesis, dysarthria, pupillary abnormalities, paralysis of the ocular muscles and the face; possibly he also had impaired vibratory and position senses, and he had mesencephalic seizures. Perhaps it is not too farfetched to assume that his visual hallucinations were due to circulatory disturbances in the posterior cerebral artery, which comes off the basilar artery. The protracted course of this man's disease, as I have learned on previous occasions, particularly from Dr. Kubik,[1] is not uncommon in thrombosis of the basilar artery. It certainly would be much more difficult to account for the fluctuations in the clinical picture, if we assume that he had a tumor. If he did, the only thing I know is that it occupied the brain stem mainly and that it was infiltrating and extended from the midbrain downward into the pons.

In summary, I am inclined to believe that this patient had a thrombosis of the basilar artery. This certainly is my first choice. I would put down zero as choice number two, three, four and five. As number six, I might record infiltrating glioma of the brain stem. Of course, I am prepared for a bitter — but instructive — disappointment.

DR. WILLIAM H. SWEET: The diagnostic operative procedures carried out on the evening of admission were the making of burr holes to exclude subdural hematoma and the taking of a ventriculogram to try to rule out the presence of an intracerebral space-taking lesion. In his electroencephalographic interpretation, Dr. Abbott stated that this patient's type of tracing might be seen with a subdural hematoma. Although our preoperative diagnosis was acute demyelinizing encephalopathy or acute multiple sclerosis, we considered it necessary to do our best to make certain that we were not overlooking the diagnosis of some disorder amenable to specific therapy.

CLINICAL DIAGNOSIS

Acute demyelinizing encephalopathy?

DR. MICHELSEN'S DIAGNOSIS

Thrombosis of basilar artery.

ANATOMICAL DIAGNOSES

Thrombosis of basilar artery.
Infarction of pons.

PATHOLOGICAL DISCUSSION

DR. CHARLES S. KUBIK: The patient did poorly postoperatively and died soon afterward.

Post-mortem examination disclosed thrombosis of the basilar artery and a superimposed distal thrombus, with infarction of the base of the pons, as illustrated in Figure 1. There were several stages of thrombus formation and organization. A small part of the thrombus was adherent and organized. The rest of it was nonadherent, and the most distal portion was quite fresh. There were anatomical variations consisting of a rudimentary vertebral artery and an anomalous posterior cerebral artery, which arose from the right internal carotid artery and was connected with the basilar artery by a

narrow, rudimentary vessel. Anatomical variations such as these are fairly common, and are sometimes responsible for a modification of the customary effects in embolism or thrombosis. The infarction of the base of the pons corresponded to the region supplied by the paramedian and possibly short circumferential branches of the occluded segment of the basilar artery.

The history and findings, as Dr. Michelsen has stated, are fairly typical of occlusion of the basilar artery.[1, 2] Headache, loss of consciousness, small pupils, ocular paralyses, dysarthria, anarthria, difficulty in swallowing, paresis or paralysis of the arms and legs and bilateral extensor plantar reflexes are commonly observed in these cases. There is often asymmetrical involvement of the two sides, and a crossed paralysis of cranial nerves on one side and limbs on the opposite side is quite common.

Temporary remissions of symptoms are not at all unusual. It seems likely that a mural thrombus in the basilar artery may at first occlude one of the small branches supplying only a small region of the pons and so result in comparatively mild symptoms followed by improvement. Then as the thrombus enlarges the basilar artery itself or more of its branches, or both, become occluded, and there is an exacerbation of the symptoms. Because of the collateral circulation through the posterior communicating arteries there may be a serious impairment of circulation in only a restricted region of the pons even with complete occlusion of the basilar artery. With either thrombosis or embolism there is commonly, though not always, superimposed thrombus formation proximally or distally, or both, which results in further infarction. We have had cases of embolism to the bifurcation of the basilar artery with softening in the midbrain, as a result of the primary embolic occlusion, and more recent infarction, before the stage of softening, in the occipital lobes and optic thalami, presumably as a result of thrombus formation in the posterior cerebral arteries and blocking of the posterior communicating arteries.

In the case under discussion there was no lesion of the midbrain, which receives a large part of its blood supply through a number of small branches from the bifurcated, terminal portion of the basilar artery and posterior cerebral arteries, all of which were patent and in communication with the collateral circulation. It is more than likely, however, that the circulation of the midbrain was seriously disturbed for a time before the collateral circulation became fully effective, thus accounting for loss of consciousness and attacks of extensor rigidity.

DR. MICHELSEN: Did you find any evidence of disease in one of the occipital lobes?

DR. KUBIK: Not on the gross examination. We do not have microscopical sections of the occipital lobes or other parts of the cerebral hemispheres, but the posterior cerebral arteries, which supply the occipital lobes, were not blocked off.

DR. MICHELSEN: And the hallucinations?

DR. KUBIK: I have no explanation for the hallucinations and doubt whether they were related to the terminal condition. It is rather interesting that unconsciousness is a common symptom even when there is no lesion of the cerebral hemispheres. The loss of consciousness may be transient, as in this case. I suppose that when the occlusion first takes place the circulation of the hypothalamus or possibly of the entire brain may be thrown into a state of serious disorder for a time.

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2. Case Records of the Massachusetts General Hospital (Case 28482). *New Eng. J. Med.* **227**:844-848, 1942.

CASE 36092

PRESENTATION OF CASE

A seventy-three-year-old woman was admitted to the hospital complaining of intermittent constipation and diarrhea.

Four years before admission she was seen in another hospital, where a right colectomy and an ileotransverse colostomy were performed. The diagnosis was carcinoid of the terminal ileum, with extension into the mesentery. Following an uneventful recovery she felt fine except for periods of constipation followed by "explosive" diarrhea. These complaints persisted but were not of sufficient severity to cause her to seek medical attention. Approximately three months before admission the symptoms began to increase progressively in severity. Examination of her stool at that time was positive for blood and *Ascaris lumbricoides*. She never noted gross blood in her stool.

Physical examination showed a well developed, well nourished woman. The heart and lungs were normal. There was a long right-rectus-muscle abdominal scar, the lower end of which (situated midway between the umbilicus and the pubis) was tender. Gas-filled loops of bowel were palpated beneath this tender area. Just above the umbilicus a tender, firm, roll-like mass was palpated. There was moderate ankle edema.

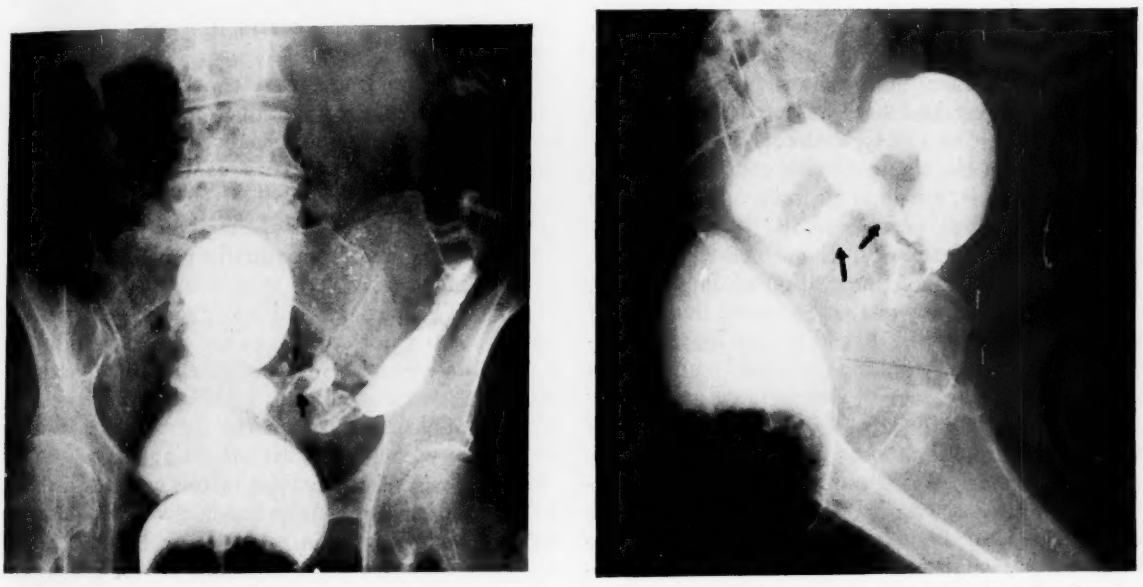
The temperature was 98.6°F., the pulse 90, and the respirations 20. The blood pressure was 180 systolic, 110 diastolic.

Examination of the blood showed a hemoglobin of 13.0 gm. and a white-cell count of 9000. A urinalysis was negative. The stools were negative for blood, parasites and ova. The serum nonprotein nitrogen was 21 mg. per 100 cc. Barium enemas revealed a 5-cm. length of narrowing in the mid-sigmoid. Its appearance suggested the possibility of an intramural, extramucosal lesion in some portions al-

though in other portions there may have been some obliteration of the mucosal pattern, with possible ulceration. Just proximal to the area of narrowing a number of tiny serrations, which had the appearance of superficial ulcerations, projected from the bowel margin (Fig. 1*A* and *B*). A radiogram of the chest revealed emphysema of the lungs and enlargement of the ventricles of the heart. An intravenous pyelogram was negative. An electrocardiogram was reported as showing incomplete right-bundle-branch block.

On the eighth hospital day an operation was performed.

There were two x-ray examinations done two days apart. At the first examination, the barium went only into the lower sigmoid; the rectum appeared normal, but in the lower sigmoid there was definite obstruction and no barium passed beyond it. The examiner either was afraid to give more barium or more likely he could not give any more barium because the patient could not retain the enema any longer. The end of the barium column does not show the pattern of tumor but of mucosal folds. That does not rule out a tumor; it may mean that the actual tumor had not been reached by the barium and that the obstruction started below the site of tumor in the bowel lumen. It is interesting that air filling in the descending colon becomes rather minute where it reaches the sigmoid — in other words, there is a gap between the descending colon and the sigmoid. At the examination two days later it was possible to get some barium beyond the area of obstruction — I say area because the pathology extends over quite a distance. The obstruction starts at the point just discussed, which is visible on the lateral view (Fig. 1*B*) and extends into the upper sigmoid close to the descending colon. The loops of sigmoid never rise out of the pelvis on any of the films, and I suspect that they were fixed in that position. If they were fixed and the sigmoid was twisted, I am sure that the examiner had quite a bit of difficulty in separating the loops to obtain an accurate opinion about the actual shape of the sigmoid. The area of obstruction is at least 10 cm. long; I cannot say how much



A B

FIGURE 1. *Area of Marked Narrowing in the Midsigmoid with a Defect Suggesting a Lesion Largely Mucosal in Location.*

DIFFERENTIAL DIAGNOSIS

DR. RICHARD SCHATZKI*: When a radiologist discusses one of these cases, he is given the films in addition to the abstract ahead of time. As has been pointed out before at these conferences, we radiologists are at a disadvantage since we have to interpret films that someone else has taken. Someone else has fluoroscoped and palpated the patient and has taken the spot films at a time that he thought was the most appropriate. That is an old complaint, which we cannot get around in a conference of this kind. It is particularly annoying in films of the sigmoid, where the loops are so foreshortened and overlying each other that one is completely at the mercy of the fluoroscopist and has to depend on the films that he took.

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longer it is because there is too much foreshortening but I expect it to be longer on account of the twisting of the sigmoid. The outline of the sigmoid is irregular mainly on the lower wall, whereas the upper wall does not appear to be so irregular. There is one area that is hardly filled with barium at all. There is no place where I can see any ulceration. That is as far as I can go on the films.

Now let us return to the history. The patient supposedly had a carcinoid of the terminal ileum removed four years previously. We shall accept that as a fact. She had been having some symptoms since that time. The first question is, Should I disregard the history completely and assume that this sigmoid lesion had nothing whatsoever to do with the carcinoid that had been resected? Could this lesion have been of the type that most commonly forms tumors in the sigmoid, with constipation and diarrhea — that is, a primary carcinoma of the sigmoid? The lateral view presents a picture that resembles polypoid tumor in the sigmoid. As far as I can decipher the conglomeration of loops there, I think that the mass was not a true tumor but a pseudotumor formed by two different loops of sigmoid and that actually no polypoid tumor was present. In the absence of definite intrinsic tumor masses and of definite areas of ulceration, we have to say that a primary tumor of the sigmoid is very unlikely. A marked deformity of the sigmoid extending for such a long length of the bowel, which is more pronounced on one side and without demonstrable ulceration, is most probably caused by something that is primarily outside the sigmoid. Various diseases could produce such a deformity. One possibility is an ovarian carcinoma, which grows around the sigmoid and deforms it. Another possibility is diverticulitis that produced marked fibrosis around the sigmoid, possibly in the wall of the sigmoid below the mucosa and possibly with an abscess. Another disease that might produce a similar appearance is endometriosis. I think we can forget about that in a woman of this age, although I think I am right in saying that occasionally women past the menopause can have an endometrial sarcoma.

Dr. Tracy B. Mallory: Very rarely.

Dr. Schatzki: I think we had better forget about that possibility.

Could this have been extension from the previous carcinoid or another independent carcinoid of the sigmoid? Carcinoid of the bowel usually produces an iceberg-like appearance, part of the tumor, usually the smaller part, protruding into the lumen and the major part being outside the lumen. Carcinoids are very likely to produce kinking of the attached bowel, resulting in a post-horn-like deformity. All this would go with the lesion as described. I do not remember having seen a carcinoid of the sigmoid. I think I have seen one of the rectum. I do not see any reason why the tumor should not appear in the sigmoid. I would say that the extent of the lesion would be quite unusual, at least for the carcinoids I have seen. Another consideration that appears to me to speak very much against that disease is the fact that the bowel in the involved areas follows a very irregular course, which does not make just one kink but changes its course several times. It seems that that would be an unusual occurrence with carcinoid.

Then we are left with the possibility of diverticulitis and ovarian carcinoma. As far as the ovarian carcinoma is concerned, I would say there is nothing on the films that is not compatible with the diagnosis of ovarian carcinoma. How about diverticulitis? There are a few points against this diagnosis. One is the fact that I do not see any diverticula. It is very dangerous to make a diagnosis of diverticulitis in the absence of demonstrable diverticula. They are very commonly not visible in the areas of marked diverticulitis because they are fibrosed or the necks of the diverticula are closed off owing to edema, but usually proximal and distal to the most involved area some diverticula are visible. The patient had no fever or leukocytosis, but that does not speak against the diagnosis. The x-ray films, except for the absence of diverticula, could very well go with a diagnosis of diverticulitis. The palpable mass and certainly tenderness under the skin are consistent with the diagnosis.

The *Ascaris lumbricoides* in the stools, I believe, is a "red herring." Ascaris can give definite filling defects in the gastrointestinal tract, particularly if they occur in large masses, but I do not believe this type and degree of obstruction can occur from ascaris worms. I am certain that this lesion was not produced by *A. lumbricoides*.

To summarize, I think that this patient had a lesion in the sigmoid that, from the evidence we have at hand, did not arise from the mucosa of the sigmoid, and that most of the changes were produced by something on the outside of the sigmoid, either a malignant tumor such as ovarian carcinoma or diverticulitis.

Dr. Walter S. Kerr, Jr.: Do you place any significance on the fact that she had continued symptoms from the time of her first operation as far as a diagnosis of ovarian carcinoma is concerned?

Dr. Schatzki: Yes; it would be a little difficult to see how a surgeon who did such an extensive operation could have missed ovarian carcinoma that was causing symptoms at the time of operation. As far as the duration of the disease is concerned, it is compatible. I think a patient may have ovarian carcinoma for four years and still be in fairly good clinical condition.

Dr. Jacob Lerman: I would like to ask Dr. Schatzki if a partial volvulus could produce an x-ray picture of that sort?

Dr. Schatzki: No; I do not think so. There are many things that would be against it. During my enumeration of possibilities, I should have mentioned

that when I said diverticulitis I included other inflammatory processes. For example, a smoldering pelvic abscess around a sponge left in at the previous operation could produce a very similar appearance.

DR. KERR: She had another operation — a repair of a ventral hernia — twelve to fifteen months after her colon was removed.

DR. SCHATZKI: The only thing I could connect with that additional information would be along the same line as what I just said about other types of chronic inflammation, possibly foreign body.

CLINICAL DIAGNOSIS

Carcinoma of sigmoid.

DR. SCHATZKI'S DIAGNOSIS

Malignant tumor involving sigmoid from outside, ovarian carcinoma?
Diverticulitis?

ANATOMICAL DIAGNOSIS

Metastases from carcinoid of ileum, involving sigmoid, mesenteric lymph nodes and liver.

PATHOLOGICAL DISCUSSION

DR. MALLORY: This patient was operated upon by Dr. Linton, who found a tumor mass in the region of the sigmoid that also involved the ovaries. He was unable at the time of operation to decide whether the tumor was intraluminal or was involving the intestine from the outside. He also found some metastases in the liver. He therefore did not do an extensive operation but merely resected the obstructed area and removed both ovaries. The pathological specimen showed that this was a carcinoid, and our impression was that it represented recurrence and metastasis of the original tumor rather than a second focus of tumor primary in the sigmoid. Carcinoids have been seen in virtually all levels of the intestinal tract, but the sigmoid would be an unusual spot.

DR. ROBERT R. LINTON: Dr. Mallory, can you explain to me the difference between a carcinoid with metastases and invasion of organs such as this patient had, and what we ordinarily think of as carcinoma, say Grade I? Why is this lesion, under the circumstances in which we found it, not considered to be a malignant one?

DR. MALLORY: Although the manner of growth of these tumors is that of a carcinoma, the type of cell is entirely different, and there are various microchemical differences that prove that they are not carcinomas. The tumor cells frequently contain granules that stain black with silver; they also contain small droplets of fat and sometimes an orange-colored pigment. In this particular case pigment was present, but we did not get a positive argentophil reaction.

Although the microscopical appearance of carcinoids is identical in various portions of the intestinal tract, their behavior seems to depend upon the site of origin. In the appendix they are almost invariably benign. In other parts of the intestinal tract they frequently metastasize. Pearson and Fitzgerald* recently reported 38 per cent of metastases in extra-appendiceal carcinoids. Even when liver metastases are present, however, as in this case, extensive resections are justified because of the slow rate at which many of these tumors grow.

DR. LINTON: I am sure there are those in the audience who wonder why I removed both ovaries at the time of the operation, as well as resecting the sigmoid lesion. I must admit that I do not have very scientific evidence for thinking that castration in this case would have helped the patient very much if at all. However, I remember a woman in her forties whom I explored for an abdominal neoplasm in 1933. At operation the abdomen was full of malignant tumor. It seemed that there was nothing I could do except a castration, and I therefore did it. I was criticized for doing it, but I felt exonerated when I was informed that she recently walked into our Tumor Clinic in 1947 apparently a well woman. It is experiences such as this that made me believe that it might be worth while to castrate this patient, especially since her uterus and ovaries appeared to be those of a woman of thirty-five or forty years of age instead of seventy-three years. It is very unlikely, of course, that carcinoid will respond the way that some of the other malignant lesions will, but I could see little harm, if any, in removing the ovaries in this elderly patient and there was just the faint possibility that it might help her.

DR. KERR: Was the lesion in the sigmoid a metastasis?

DR. MALLORY: We believe it was.

DR. SCHATZKI: Was the mucosa involved or not?

DR. MALLORY: The wall of the bowel was extensively involved, and the disease had spread to the mucosa but not through it at any point.

DR. KERR: Dr. Dobyns has seen quite a few of these in the Mayo Clinic and believes that the possibility was that she had this tumor in the sigmoid at the time of the right colectomy, for her symptoms had persisted after the original lesion was removed. Since the sigmoid resection, the constipation and diarrhea have practically disappeared.

DR. MALLORY: I cannot rule out that possibility but the appearance to us suggested very much more involvement of the sigmoid from outside rather than from within.

*Pearson, C. M., and Fitzgerald, P. G. Carcinoid tumors: reëmphasis of their malignant nature. *Cancer* 2:1005-1026, 1949.

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FROM "ANIMAL MAGNETISM" TO ELECTROPHRENIC RESPIRATION

The development of the electrophrenic respirator by Sarnoff and Whittenberger at the Harvard School of Public Health has introduced both a means of therapeusis and a device for studying some of the basic problems in the regulation of respiration in health and in disease.[1]

The application of an electric current to the phrenic nerve was attempted as early as 1793 by Hufeland in Göttingen, Germany, two years after Galvani had recorded his observations on "animal magnetism" and the power of metallic contacts to move the muscles of a dead frog. Thus, ever since the publication of *De viribus electricitatis*, sporadic attempts have been made to produce artificial respiration by galvanic stimulation of the nervous system. An excellent description of these early efforts is given in the section on artificial respiration in the book *Chloroform* by Sansom,[2] published in 1866, as well as an account of successful "galvanism of the phrenic nerve" performed almost a century ago:

> A boy, aet. 4, in the course of chloroform-administration assumed all the appearances of threatened death. The face became livid, the pulse ceased, the jaw dropped, the appearance was exactly that of a corpse, and all the by-standers thought that life was extinct. Artificial respiration was immediately commenced, with methodical compression of the chest. Then Dubois-Reymond's galvanic apparatus was sent for. One pole was placed over the situation of the origin of the phrenic nerve (where the omo-hyoid muscle crosses the sterno-mastoid), the other was applied to the seventh intercostal space. Contraction of the diaphragm followed. The proceeding was intermitted and repeated, to imitate natural respiration, and after a time a slight spontaneous pulse became perceptible. Methodical compression of the chest-walls was again concurrently resorted to, and in time recovery became complete.

Modern researches have likewise amply demonstrated that the rate and depth of respiration can be electrically influenced within wide limits and that even a refined control of breathing can be obtained if the relative duration of inspiration is adjusted to the total respiratory cycle.

That spontaneous respiration could be suppressed during stimulation of the phrenic nerve in the dog was observed in 1936 by Brigenti,[3] who also demonstrated the role of the vagus nerve in this reflex inhibition. The fact has been confirmed in five different species of animals, as well as in unanesthetized human beings, and is among the most interesting of the findings that are currently being investigated. It has at least one important clinical application. By this procedure the respiratory center of the patient with bulbar poliomyelitis who has gross irregularity and inco-ordination of breathing is suppressed. An effective and even type of respiration that brings about an adequate exchange of oxygen and carbon dioxide in the lung is possible of therapeutic achievement.

Sarnoff and Whittenberger emphasize that the electrophrenic respirator is no substitute for the tank respirator in poliomyelitis but is indicated when the latter is unable to function effectively because of poorly synchronized or irregular breathing. By temporary suppression of the respiratory

center a decrease in its sensitivity may be brought about as arterial carbon dioxide is reduced by effective, electrically controlled respiration. With equilibrium restored, the patient may be cared for in the conventional tank type of respirator. In the spinal form of the disease when the phrenic nerves do not respond adequately to stimulation, it is evident that the electrophrenic respirator is of no value.

The rationale for use of the electrophrenic respirator in the respiratory depression or paralysis of high spinal anesthesia is enhanced by experiments suggesting that electrophrenic respiration does not further depress the circulation under these circumstances but rather tends to elevate the arterial blood pressure. Depression of the circulation has been shown to occur during the conventional positive-pressure method of treating this type of operating-room catastrophe.[4]

With practice, electrophrenic respiration can be readily performed on normal newborn infants; 1 apneic infant has been treated for ten minutes with the electrophrenic respirator, after which spontaneous respiration occurred. Apnea of intracranial hemorrhage or injury has been corrected by means of electrophrenic respiration for varying periods up to fifty-two hours, and it is theoretically superior to positive-pressure breathing during intracranial surgery because the latter is known to increase peripheral and intracranial venous pressure whereas the former tends to decrease it by virtue of utilizing the inspiratory action of the thorax. Certainly, the success of investigations done to date warrants further study of the possible usefulness of the electrophrenic respirator in other kinds of respiratory arrest and after drowning, electrocution, asphyxia and the like.

The Department of Physiology of the Harvard School of Public Health plans to sponsor a short course in the spring for those interested in the use of the electrophrenic respirator since previous experience in finding the motor point of the phrenic nerve in the neck of normal patients or volunteers is desirable before the attempt is made to use the apparatus in an emergency.

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RED CROSS APPEAL

The March Fund Campaign of the American Red Cross is not only an appeal for support for the various Red Cross services but also a résumé of the activities of the organization in times of disaster and in times of peace.

Perhaps the most significant of these services is the widely acclaimed blood program, which President Truman believes "may well become the greatest single health activity in history." At the end of the first year and a half of its operation, the Red Cross Blood Program had 28 regional blood centers, with 32 attached mobile units serving areas of population totaling 40,000,000. Establishment of 15 additional regional centers during the current fiscal year is expected, and it is anticipated that by the end of that period, blood collected from voluntary donors will have been distributed to nearly 2000 hospitals. In Massachusetts it has been recognized that the Red Cross is "the only logical agency" to assume responsibility for "perpetual preparedness for a local or nation-wide catastrophe, and the making available of blood to all who may need it in any hospitals, without charge for the product."*

Other activities of the Red Cross include services to the armed forces (nearly $20,000,000 being budgeted for this purpose in 1949–1950), highway first aid (with 185 highway first-aid stations in 19 states), water safety (courses in swimming and life saving, with 677,368 certificates issued during the fiscal year 1948–1949), gift boxes sent by American Junior Red Cross members to war-damaged schools overseas, disaster service (1,572 nurses served in Red Cross operations in 72 disasters affecting 32

*Editorial. Massachusetts Blood Program. *New Eng. J. Med.* **242**: 34, 1950.

states in the fiscal year ending June 30, 1949), accident prevention (1,845,678 children in primary and elementary grades received instruction in accident prevention in the 1948–1949 school year) and help in Veterans Administration hospitals (an average of more than 20,000 trained volunteers assisted these hospital staffs to carry out medical, recreational and welfare programs).

There is no question in anyone's mind that the activities enumerated are vital and must continue. They can do so only with active co-operation and financial support of the citizens throughout the country, who will be justly proud of the fact that their efforts guaranteed the continued existence of the American Red Cross and the services it renders.

MENTAL HEALTH IN MASSACHUSETTS

It is a disturbing sign of the times that sympathy and widespread curiosity do not always go hand in hand with constructive effort. In Massachusetts the paradox has taken such forms as the conclusive vindication of Dr. Miriam Van Waters (and, presumably, of her principles of penology) along with the presence on the statute books, nearly a year later, of the obsolete and often inhumane laws pertaining to female delinquency.[1] No less remarkable is the ironic fact that, in spite of general public and professional interest in psychiatry and the more dramatic aspects of psychoanalysis, preventive and therapeutic efforts in mental health have never been in greater need of encouragement and financial support. The disparity between the salaries and the abilities of psychiatrists in the public service of the Commonwealth is so great that the Commissioner of Mental Health may resign, to accept a similar position in Maryland, and there is a danger that psychiatrists in important positions in state hospitals will also resign; worse still, there is grave concern lest the law providing for business managers for the state hospitals be used for political purposes. The services for mentally handicapped children in the Commonwealth are limited.[2] This grave situation is permitted to exist in a community in which, it has been estimated, 23,000 adults are patients in mental hospitals.[3]

In the light of these facts, the growth of the Massachusetts Society for Mental Hygiene, established in 1913, and the increasing effectiveness of its efforts merit the attention and interest of all physicians in the Commonwealth. The work of this organization is largely educational, one of its primary purposes being to influence people to consider mental disease as rationally as they think of physical illness and to seek help early enough for treatment to be effective. In addition to providing speakers on mental health, the Society distributes a variety of pamphlets (both its own publications and those of the National Committee for Mental Hygiene) giving information on mental health. It also employs radio broadcasts and issues press releases on this subject. Churches, schools, parents' groups, librarians and other social agencies receive encouragement and leadership from the Society in their efforts for better mental health. Last year the Society circulated 80,000 copies of Commissioner Perkins's excellent annual report setting forth the needs of the state hospitals for larger appropriations, and it is believed that this effort prompted the public to exert pressure on legislators, resulting in the increased allocations desired.

To continue its activities at the present level through 1950, the Society must obtain $25,000 in contributions outside the Greater Boston area (it has been a member of the Community Fund since 1935, but the Fund is unable to increase its grant in proportion to the Society's expanding program). The officers of the Society hope that all who are interested in better mental health, including those whose relatives or friends have suffered from nervous and mental illness, will make up the amount necessary to the organization's continued efficient functioning.

The existing inadequacies in the provision of psychiatric facilities in the Commonwealth, together with the danger of a lowering of standards because of insufficient pay and the hazard of political interference, demand a vigilant organization to keep the public aware of the gravity of the situation. The Massachusetts Society for Mental Hygiene has amply demonstrated its ability to handle such a problem. It would be deplorable

if insufficient contributions and support caused the Society to fail in its efforts to obtain for the state psychiatrists a rate of pay proportionate to their training and abilities and provision, in general, for mental-health facilities commensurate with the dignity of the Commonwealth.

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FREE PENICILLIN FOR SUBACUTE BACTERIAL ENDOCARDITIS

In October, 1948, the Massachusetts Heart Association (then the New England Heart Association) set aside a portion of the fund raised during the heart campaign to provide free penicillin for the treatment of subacute bacterial endocarditis. This was intended only for patients who could not afford the drug and to whom other resources (insurance or welfare funds) were not available. A special penicillin committee was appointed to approve requests and supervise the disbursement of the fund.

During the first year, 27 of 28 requests for penicillin were approved. Of 22 patients whose condition was known two months or more after the completion of treatment, 21 were alive and believed to be cured.

The amount of penicillin approved for treatment varied from the recommended amount of 1,000,000 units a day for thirty days, which was used for the majority of the patients, to 8,000,000 units a day for an exceptional patient. The cost of the penicillin has averaged $153 per patient.

The program appears to supply a definite need, and will be continued in 1950. Requests for streptomycin and aureomycin will be approved when these drugs are indicated in the treatment of subacute bacterial endocarditis. Requests for free penicillin should be made to the Massachusetts Heart Association by the physician in charge of the patient and by the hospital superintendent.

The Vapor Bathing Institution, Cambridge St., in Boston, under the control of Drs. Miles and Fogg, appears to meet the approval of practitioners generally.

Boston M. & S. J., *February 27, 1850*

MASSACHUSETTS MEDICAL SOCIETY

NEW SECTION APPROVED

The Council of the Society having approved the formation of a new section on diseases of the eye, ear, nose and throat, Dr. James J. Regan, of Boston, and Dr. Lawrence R. Dame, of Greenfield, have been appointed chairman and secretary respectively.

The objectives of this Section are "the dissemination of knowledge concerning these special fields to the general and special physicians, the providing of a sounding board for an interest in and contact with policies of the parent Society, and the establishment of fellowship."

The first meeting of the Section will be held at a luncheon at 12 noon on Wednesday, May 17, 1950, in the Hotel Statler, Boston, at the time of the annual meeting of the Massachusetts Medical Society. An excellent program has been arranged, and all interested physicians are urged to attend.

Lawrence R. Dame, *Secretary*
Section on Ophthalmology and Otolaryngology

DEATHS

Fitzgerald — Clara P. Fitzgerald, M.D., of Worcester, died on November 3. She was in her seventy-fourth year.

Dr. Fitzgerald received her degree from Woman's Medical College of Pennsylvania in 1903. She was a member of the staff of St. Vincent Hospital and a member of the New England Dermatological Society and the American Academy of Dermatology and Syphilology.

A sister survives.

King — Francis G. King, M.D., of Quincy, died on February 8. He was in his fiftieth year.

Dr. King received his degree from Georgetown University School of Medicine in 1930. He was a former treasurer of Norfolk South District Medical Society and was a member of the surgical staff of Quincy City Hospital and the staff of St. Margaret's Hospital, Dorchester. He was also a member of the International College of Surgeons and the New England Obstetrical and Gynecological Society and a fellow of the American Medical Association.

His widow and a daughter survive.

Vinal — Charles R. Vinal, M.D., of Turners Falls, died on October 15. He was in his sixty-ninth year.

Dr. Vinal received his degree from Harvard Medical School in 1907. He was a member of the staffs of Franklin County Public Hospital in Greenfield and Farren Memorial Hospital in Montague City and was a fellow of the American Medical Association.

His widow survives.

NOTES FROM THE MEDICAL EXAMINER*

CRIMINAL ABORTION

Abortion, legally defined, is the premature expulsion of the fetus before the term of gestation is complete. The law does not differentiate abortion, miscarriage and premature delivery. Criminal abortion is the unlawful expulsion of the fetus by artificial means. It is a felony when any person advises, assists in or performs an abortion. Some states place self-induced abortion in a similar category. Death of the mother upon whom an abortion has been performed is homicide. Physicians failing to report known or suspected cases of abortion are open to suspicion of complicity and technically to criminal prosecution. It is a felony under common law not to report a crime to proper authorities — that is, the district attorney or the police, and when a death results, the medical examiner.

Incidence

Accurate information is difficult to obtain. Induced abortion probably occurs more frequently than hospital records indicate.[1] It is believed that 1 in every 3 to 6 pregnancies terminates by abortion.[2] Therapeutic abortions constitute a small fraction of these. Estimates of the relative incidence of induced and spontaneous abortion vary from 1:1 to 2:1.[3] Half or more of induced abortions are believed to have been the act of someone other than the mother. Serious complications from spontaneous abortion are rare,[4] whereas induced abortion is responsible for a disproportionately high incidence of all puerperal deaths, about 30 per cent.[5]

Methods and Morbidity

The methods are numerous and frequently bizarre. The procedure varies with the knowledge and skill of the abortionist and the stage of pregnancy. Most abortions are attempted before the fourth month of gestation.[3] There are three main classes: application of general violence; use of ecbolic drugs and systemic poisons; and local mechanical and chemical violence.

General Violence

It is a popular misconception among lay people that gymnastics, severe exercises, external trauma to the lower abdomen, hot baths and so forth can induce abortion. Successful abortion after these procedures is fortuitous. In the vast majority of cases abortion is spontaneous and caused by a preexisting abnormality of fetal or maternal tissues.[6] Unless trauma is so severe as to produce serious injury or death of the mother, none of these measures are successful.

*Presented by the Department of Legal Medicine, Harvard Medical School.

Drugs and Chemicals

Drugs commonly used as ecbolic agents are purgatives, emetics, essential oils, quinine and ergot. Even at toxic doses, none of these have true abortifacient properties in the first two trimesters of pregnancy. Often the dose is increased when the desired effect is not obtained. The result may be systemic poisoning, especially when the essential oils are employed. Many metallic poisons, such as lead, arsenic and mercury, and a variety of organic substances are used as abortifacients. Although pregnancy may be terminated by these means, the mechanism is indirect. The maternal organism has to be so poisoned that support of the fetus fails. This means systemic intoxication and frequently death. The fetus is fully as resistant to the effect of any known chemical substance as the mother.

Local Injury

Chemical. The aim is introduction of an irritating or escharotic substance into the endometrial cavity. Use of the bulb syringe requires considerable pressure if projection of fluid into the uterine os is to occur. Pressure alone may be sufficient to force liquid through the endometrium into the uterine tissues, and extensive chemical necrosis may follow use of even soap solution. If the fluid is mixed with air, entrance of the latter into veins may lead to fatal air embolism. Alkaline soap pastes — such as Utra jel, Leunbach's paste, Interruptin and Antigravid — may cause extensive local damage[7] or rapid death from hemorrhagic pulmonary edema[8] if the endometrium is penetrated by the syringe used in injection. Instillation of necrotizing chemicals, including phenols, corrosive acids and alkalies, and metallic salts have been disastrous on many occasions. The strong corrosive may lead to rapid death from shock. Absorption of toxic chemicals through the richly vascular decidual bed may give rise to systemic poisoning. Fatal intravascular hemolysis following a potassium permanganate douche has been reported.[9] Insertion of permanganate wafers intravaginally, although rarely terminating pregnancy, regularly leads to local hemorrhage and cicatrizing injury.[10]

Mechanical. Instrumentation varies from dilatation and curettage practiced by the skilled abortionist to the crudest attempts by the mother or an ignorant layman. Some abortionists merely initiate the abortion and leave the subsequent care and treatment to the unsuspecting physician. The principal complications are infection and hemorrhage, either of which may occur in the absence of significant wound production. Simple dilatation of the cervix is done by both amateurs and professionals by the introduction of such objects as sponges, slippery-elm sticks, sounds, catheters and bobby or safety pins. Death is uncommon accord-

ing to vital statistics. Long, slender instruments, such as wire, umbrella stays, paper knives and knitting needles, are sometimes inserted. This appears more dangerous than records suggest. A serious complication is laceration and perforation of the uterus — indeed, the most extensive and mutilating injury may be inflicted.

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MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JANUARY, 1950

Résumé

Diseases	January 1950	January 1949	Seven-Year Median
Chancroid	2	10	2*
Chicken pox	2101	4154	2322
Diphtheria	21	35	18
Dog bite	631	611	508
Dysentery, bacillary	16	1	10
German measles	77	142	142
Gonorrhea	198	266	360
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	1	3	1*
Malaria	1	0	8
Measles	260	6024	1647
Meningitis, meningococcal	5	5	18
Meningitis, Pfeiffer-bacillus	5	4	4
Meningitis, pneumococcal	7	3	5
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	1	0
Meningitis, undetermined	6	5	6
Mumps	1179	1633	1113
Poliomyelitis	1	0	1
Salmonellosis	2	3	4
Scarlet fever	416	1012	1012
Syphilis	147	194	358
Tuberculosis, pulmonary	239	194	213
Tuberculosis, other forms	15	12	12
Typhoid fever	1	0	0
Undulant fever	3	3	2
Whooping cough	496	304	480

*Six-year median.

Comment

Diseases above the seven-year median were diphtheria, bacillary dysentery and mumps. None of those diseases showed marked increases.

Diseases below the seven-year median were German measles, measles and scarlet fever. The incidence of chicken pox and mumps was about equal to the seven-year median.

At long last poliomyelitis has fallen to the seven-year median — 1 case in January!

Again this month, measles was at a very low prevalence. Previous low levels in January were in 1945 (260 cases) and in 1907 (257 cases).

Scarlet fever continued at an unusually low level for the seventh consecutive month. The January prevalence was only 1 case above the record low of 415 cases in 1948.

Geographical Distribution of Certain Diseases

Diphtheria was reported from: Boston, 10; Brockton, 1; Cambridge, 3; Chelsea, 2; Danvers, 1; Lawrence, 1; Norwell, 1; Somerville, 1; Tewksbury, 1; total, 21.

Dysentery, bacillary, was reported from: Belchertown, 5; Boston, 7; Worcester, 4; total, 16.

Infectious hepatitis was reported from: Wellesley, 2; total, 2.

Malaria was reported from: Boston, 1; total, 1.

Meningitis, meningococcal, was reported from: Boston, 4; Lynn, 1; total, 5.

Meningitis, Pfeiffer-bacillus, was reported from: Boston 1; Everett, 1; Lowell, 1; Lynn, 1; Milford, 1; total, 5.

Meningitis, pneumococcal, was reported from: Abington, 1; Boston, 1; Fall River, 1; Freetown, 1; Holyoke, 1; Lynn, 1; Watertown, 1; total, 7.

Meningitis, undetermined, was reported from: Ayer, 1; Haverhill, 2; New Bedford, 1; Pittsfield, 1; Swansea, 1; total, 6.

Poliomyelitis was reported from: Taunton, 1; total, 1.

Salmonellosis was reported from: Fall River, 1; Salem, 1; total, 2.

Septic sore throat was reported from: Arlington, 2; Boston, 6; Fall River, 1; Foxboro, 2; Melrose, 2; Newton, 1; Westford, 1; Worcester, 2; total, 17.

Trichinosis was reported from: Ayer, 1; total, 1.

Typhoid fever was reported from: Williamstown, 1; total, 1.

Undulant fever was reported from: Bridgewater, 1; Hanson, 1; Randolph 1; total, 3.

CORRESPONDENCE

THE FAMILY DOCTOR AND BLUE SHIELD

To the Editor: The excellent introduction and discussion of the report of the subcommittee on Blue Cross–Blue Shield Problems at the recent meeting of the Council of the Massachusetts Medical Society was so informative and the subsequent comments and action so constructive that little additional comment appears necessary. However, two of the points made in the discussion appear important enough to warrant emphasis.

In the first place, because successful expansion of Blue Shield will cause doctors' incomes to be increasingly derived from Blue Shield remuneration, every care should be taken to protect the adequacy of payments to doctors for services rendered under the plan and to avoid establishing precedents that may, as Blue Shield and other insurance extends, result in underpayment of doctors.

Secondly, if decisions and actions pertaining to the Blue Shield are to result in successful expansion, they should be undertaken with an affirmative point of view rather than a negative one based on opposition to a national health program.

In connection with the second consideration, the remark that Blue Shield thus far was not of great concern to the internist or family physician calls attention to a point that in my estimation deserves more attention than is commonly accorded it. Physicians intimately concerned with teaching are disturbed by the little that medical school education, and subsequent internships, do to prepare doctors as family physicians. As one watches the development of insurance such as Blue Shield, with services limited largely to hospital care, especially surgery, and the establishment of diagnostic clinics and medical-care units for certain categories of diseases such as rheumatic fever, cerebral palsy, prematurity, cancer and tuberculosis one wonders if the medical profession is doing any better than the medical school and teaching hospitals in maintaining the impor-

tance of the family physician in medical practice. The same question might be raised about the establishment of pilot screening clinics by public-health units, both in undermining the role of the family physician and in establishing undesirable precedents of inadequate remuneration of physicians.

Blue Cross and Blue Shield insurance should leave more money to the public to pay family physicians. But may it not be that such insurance schemes and the development of other services on a categorical basis tend to by-pass the family physician and so to lessen the importance of his role? If so, this would indeed appear a serious matter, for most physicians have agreed in the past and, I think, believe today that the family physician should be the backbone of medical care. It would be interesting and informative if doctors performing the important role of family physicians would express their opinions on this subject.

ALLAN M. BUTLER, M.D.

Boston, Massachusetts

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Blakiston's New Gould Medical Dictionary: A modern comprehensive dictionary of the terms used in all branches of medicine and allied sciences, including medical physics and chemistry, dentistry, pharmacy, nursing, veterinary medicine, zoology and botany, as well as medicolegal terms. Editors: Harold W. Jones, M.D., Norman L. Hoerr, M.D., and Arthur Osol, Ph.D. With the co-operation of an editorial board and 80 contributors. 8°, cloth, 1492 pp., with 252 illustrations. Philadelphia: Blakiston Company, 1949. $8.50.

The title of this dictionary speaks for itself. The text is based on the last edition of Dr. Gould's dictionary published in 1941. Thousands of new words have been added, and the compilation includes material published as late as 1947. A new, simple phonetic method of syllabification and pronunciation has been used. Eponyms and biographic names have been placed in their proper alphabetic order in the text. The tables have been assembled together in the back of the volume, and a special list of the tables precedes the dictionary proper. The usual practice is to place the tables in the text under the subjects. It would have helped if the names of foreign persons had been syllabized and accented. Many persons unfamiliar with foreign languages find it difficult to pronounce names in such languages. The volume is well published and should be in all medical and general libraries. The price is surprisingly low when the type of book is considered. One is reminded of the great scholarly work of Dr. Frank P. Foster, of Latin, English, French and German medical terms, published in four large volumes in 1888 to 1894 and still in use today as a standard reference work.

The Physician's Business: Practical and economic aspects of medicine. By George D. Wolf, M.D., assistant clinical professor of otolaryngology, New York Medical College. With a foreword by Harold Rypins, M.D. Third edition. 8°, cloth, 563 pp., with 96 illustrations. Philadelphia: J. B. Lippincott Company, 1949. $10.00.

In this new edition of a standard book the material has been completely reorganized, largely rewritten and brought up to date. Chapters on investments and on retirement have been added. The text is divided into seven parts, as follows: the doctor in the making, including internship and residency, specialization, medical careers other than private practice, selecting a location and planning and equipping an office; the management of a medical practice, including records and fees, instructions to patients, office personnel and the nurse's duties and her place as a technician in medical and surgical practice; various technics of prescribing, and the use of solutions and moulages; professional contacts, including ethical conducts, medical journalism and public speaking; the doctor and the law; finances; and socialized medicine. The material is well organized, the text well written and the book well published. The author had the benefit of the advice of experts in the special fields of law and finance. This edition is essentially a new book and should prove invaluable to both young and old physicians and should be in the reference collections of all medical and general libraries.

Hemorrhagic Disorders: A guide to diagnosis and treatment. By Paul M. Aggeler, M.D., assistant clinical professor of medicine, University of California Medical School; and S. P. Lucia, M.D., professor of medicine, University of California Medical School. 4°, cloth, 112 pp. Lettered and illustrated by Phylura Gibbs, Helene Cleare and Jean Thompson, under the supervision of Ralph Sweet. Chicago: University of Chicago Press, 1949. $10.00.

This guide is based on the experience gained by the authors in observing over 500 patients with various diseases. Concise summaries are presented in four sections on the physiology of hemostasis, the technics of hemostatic tests, the principal clinical features of disorders characterized by abnormal bleeding and the agents and procedures that are available for treatment. The material is presented in the manner of a graphic chart and should be easily understood by the practicing physician, the medical student and the laboratory technician. A bibliography of thirteen pages arranged by topics is appended to the text. The book is well published and should prove useful to those persons for whom it is intended.

Medical Clinics on Bone Diseases: A text and atlas. By I. Snapper, M.D., physician and director of medical education, Mount Sinai Hospital, New York City, and clinical professor of medicine, Columbia University College of Physicians and Surgeons. Second edition. 4°, cloth, 308 pp., with 264 illustrations. New York: Interscience Publishers, 1949. $20.00.

In this edition a standard treatise and atlas has been completely revised and brought up to date. All the chapters have been rewritten and rearranged. Chapters have been added on osteoporosis, osteoporosis circumscripta cranii, leontiasis ossea, neurofibromatosis of the bones and the skeletal lesions in lymphosarcoma, Hodgkin's disease and hemolytic anemias. The number of plates and figures has been considerably increased. Extensive bibliographies are appended to the various chapters. The plates are interspersed throughout the text with the subjects they depict — a very convenient and useful arrangement. The radiographic plates are excellent, and the book is well published. It should be in all collections on the subject and available to orthopedists and radiologists. The price is not excessive for the type of work.

The Psychoanalytic Study of the Child: Vol. III–IV. 8°, cloth, 493 pp. New York: International Universities Press, Incorporated, 1949. $10.00.

This latest volume of a special series contains twenty-five papers on the various aspects of child development in relation to psychoanalysis.

The Diagnosis of Pancreatic Disease. By Louis Bauman, M.D., assistant visiting physician to the Presbyterian Hospital, New York City. With a foreword by Allen O. Whipple, M.D. 4°, cloth, 74 pp., with 24 tables. Philadelphia: J. B. Lippincott Company, 1949. $5.00.

This monograph discusses the pancreatic-function tests and their application in diagnosis of diseases of the pancreas. It is based on work done at the Presbyterian Hospital in New York City during the past ten years and embraces about 550 determinations made with the vagus stimulant Mecholyl on patients suffering from pancreatic and nonpancreatic disease. A selected bibliography of eighty-six items concludes the text. There is a good index, and the type and printing are excellent. The book should be in all medical libraries and in all collections on the subject.

A Synopsis of Medicine. By Sir Henry L. Tidy, K.B.E., M.A., M.D., B.Ch. (Oxon.), F.R.C.P. (Lond.), extra physician to H. M. The King, consulting physician to St. Thomas's Hospital, Hon. Major-General, lately consulting physician

to the British Army. Ninth edition, revised and enlarged. 12°, cloth, 1243 pp. Baltimore: Williams and Wilkins Company, 1949. $7.50.

The *Synopsis* of Dr. Tidy has enjoyed an enviable reputation. The first edition was published in 1920, and since then there have been fourteen editions or reprintings. The material is arranged in the form of short summaries with special headings. There is a comprehensive index. The printing was done in Great Britain, and the sheets were bound in the United States.

Textbook of Virology: For students and practitioners of medicine. By A. J. Rhodes, M.D., F.R.C.P. (Edinburgh), Connaught Medical Research Laboratories and School of Hygiene, University of Toronto; and C. E. van Rooyen, M.D., D.Sc., M.R.C.P. (London), Connaught Medical Research Laboratories and School of Hygiene, University of Toronto. 8°, cloth, 312 pp., with 40 illustrations. New York: Thomas Nelson and Sons, 1949. $5.00.

This brief manual is intended as an introduction to virus diseases and diseases caused by the rickettsias. The material is based on a course of lectures delivered to students over a period of fifteen years. The publishing is excellent.

Illustrations of Surgical Treatment: Instruments and appliances. By Eric L. Farquharson, M.D., F.R.C.S. (Ed.), F.R.C.S. (Eng.), assistant surgeon, Royal Infirmary, Edinburgh, member of clinical teaching staff, University of Edinburgh, surgeon, Berwick-on-Tweed Infirmary, and assistant surgeon, Kirkcaldy Hospital. With a foreword by the late Sir John Fraser, Bt., K.C.V.O., M.C., M.D., Ch.M., F.R.C.S. (Ed.). Third edition. 8°, cloth, 391 pp., with 319 illustrations and 61 plates. Baltimore: Williams and Wilkins Company, 1949. $7.50.

Dr. Farquharson, in this new edition of his book, has thoroughly revised the text to bring it up to date. The intent of the author is to illustrate by numerous photographs practical methods of surgical treatment that are rarely found in textbooks of general surgery. An appendix of sixty-one plates is devoted to the illustration of various instruments and appliances. The type, printing and illustrations are excellent. The printing was done in Great Britain.

Operations of General Surgery. By Thomas G. Orr, M.D., professor of surgery, University of Kansas School of Medicine, Kansas City, Kansas. Second edition. 4°, cloth, 890 pp., with 721 illustrations. Philadelphia: W. B. Saunders Company, 1949. $13.50.

Dr. Orr, in this second edition of his book on operative surgery, first published in 1944, has made revisions or additions in every chapter. Illustrations have been added, and some have been replaced by drawings illustrating a more modern technic. The most important additions have been made to the chapters on the digestive system and on congenital anomalies, in which new technics are given for esophagogastrostomy, total gastrectomy, pancreaticoduodenectomy, repair of strictures of the biliary ducts, colon resection, prolapse of the rectum and the surgical treatment of anomalies of the aortic arch. References to the pertinent literature are interspersed throughout the text. There is a comprehensive index. The type, printing and illustrative work are excellent. The book covers the whole field of surgery and should be in the reference section on surgery of all medical libraries and available to all surgeons.

An Atlas of Electrocardiography. By William Dressler, M.D., cardiologist, Maimonides Hospital, Brooklyn, consultant in cardiology, The Brooklyn Hospital, and lecturer in medicine, Long Island College of Medicine, Brooklyn; and Hugo Roesler, M.D., cardiologist, Department of Medicine, and associate professor of radiology, Temple University School of Medicine and Hospital, Philadelphia. 8°, cloth, 503 pp., with 439 illustrations. Springfield, Illinois: Charles C Thomas, 1949. $14.00.

This atlas is intended for physicians who know the fundamentals of electrocardiography and the arrhythmias. The material is divided into four sections: electrocardiographic patterns (not including disturbances of rhythm); patterns of disturbance of rhythm; advances in the electrocardiographic diagnosis of myocardial infarctions; and interpretation of the electrocardiogram with the aid of unipolar leads. The explanatory text is placed opposite the tracings throughout the volume, making the atlas easy to use. In the first two sections the tracings, displaying similar patterns, are grouped together. Fifty cases with post-mortem control are included in the material presented. This excellent atlas should be in all collections on the subject and in hospital and large medical libraries.

Industrial Hygiene and Toxicology. Volume II. Frank A. Patty, editor. 8°, cloth, 1138 pp. New York: Interscience Publishers, Incorporated, 1949. $15.00.

This concluding volume of an important set describes industrial exposures and discusses the properties and physiologic action of atmospheric contaminants, permissible concentrations, inflammability and odors with warnings against toxic effects. There is a special chapter on potential exposures in industry and their recognition and control. The first volume was reviewed in the *Journal* for August 11, 1949.

Radiologic Exploration of the Bronchus. By S. DiRienzo, M.D., assistant professor of radiology and physiotherapy, and chief of the Radiology Department of the Institute of Cancer, The University of Córdoba, Argentina. Translated by Tomas A. Hughes, M.D. With a foreword by Richard H. Overholt, M.D. 8°, cloth, 332 pp., with 466 illustrations. Springfield, Illinois: Charles C Thomas, 1949. $10.75.

In this translation the work of Dr. DiRienzo on bronchography is made available to the English-reading physician and surgeon. The book is based on material originally assembled for the Fourteenth National Congress of Surgery. This material has been brought up to date, and the technic of the exploration of the bronchus is explained in detail. The first six chapters discuss the embryology, histology and anatomy of the bronchus, and bronchography in general. Then follow chapters on malformations, bronchiectasis, emphysema and asthma, carcinoma, hydatid cyst and suppuration of the lung. Lists of references are appended to the various chapters. There is a good combined index of authors and subjects. The book should be in all medical libraries and in all collections on radiology and respiratory diseases.

NOTICES

SPRINGFIELD HOSPITAL EDUCATIONAL PROGRAM

The following is the March calendar of the Springfield Hospital's Educational Program:

The first meeting, held on Wednesday, March 1, at 12:00 noon, was a Pediatric Conference entitled "Pathology of Kidney Diseases in Children," conducted by Dr. William Kaufmann in the Staff Conference Room.

Saturday, March 4. 11:00 a.m. Guest Speaker Conference. Dr. John B. Truslow, assistant dean, College of Physicians and Surgeons, Columbia University, will speak on the subject "Postgraduate Medical Education" in the Staff Conference Room.

Wednesday, March 8. 12:00 noon. Pediatric Conference entitled "Meningitis in Children" will be conducted by Dr. H. H. Shuman in the Staff Conference Room.

Saturday, March 18. 11:00 a.m. Guest Speaker Conference. Dr. Richard H. Overholt will speak on the subject "The Second Most Important Silent Lung Lesion" in the Staff Conference Room.

Tuesday, March 21. 8:30 p.m. Clinicopathological Conference. Staff Conference Room.

Wednesday, March 22. 12:00 noon. Pediatric Conference entitled "Communicable Diseases in Children" will be conducted by Dr. H. H. Shuman in the Staff Conference Room.

Wednesday, March 29. 12:00 noon. Pediatric Conference entitled "Complications of Upper Respiratory Infections in Children" will be conducted by: Dr. F. A. Mahoney in the Staff Conference Room.

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

The regular monthly meeting of the New England Society of Physical Medicine will be held in Room 6–120, Massachusetts Institute of Technology, on Wednesday, March 8, at 8 p.m. Dr. Shields Warren will speak on the subject "Therapeutic Aspects of Atomic Energy." Lantern slides will be shown.

Physicians, scientists and students are cordially invited to attend.

NEW ENGLAND DIABETES ASSOCIATION

A clinical meeting of the New England Diabetes Association will be held in the Medical Amphitheater of the Hartford Hospital, Hartford, Connecticut, on Thursday, March 9, at 2 p.m.

PROGRAM

Diabetes in Pregnancy. Dr. Burdette J. Buck.
Co-operation in the Treatment Plan for Diabetes. Dr. Samuel Donner.
Subject to be announced. Dr. Barnett Greenhouse.
Recent Advances in the Physiology of Diabetes. Dr. C. N. H. Long.

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

A meeting of the Boston City Hospital House Officers' Association will be held in the Dowling Amphitheater of the Hospital on Tuesday, March 14, at 7 p.m. Dr. Bradley L. Coley, assistant professor of surgery, Cornell University Medical College, will speak on the subject "Tumors of Bone."

All interested persons are invited to attend.

LONG ISLAND COLLEGE OF MEDICINE ALUMNI DAY

The annual Alumni Day of the Long Island College of Medicine will take place on Saturday, April 29. There will be a scientific session at Polhemus Clinic in the morning, followed by the seventieth annual dinner, to be held at the Columbus Club, 1 Prospect Park West, Brooklyn, New York, at 7 p.m. The principal speaker will be Dr. Jean Curran, president of the Long Island College of Medicine.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY, INC.

The general oral and pathology examinations (Part II) for all candidates will be conducted at The Shelburne, Atlantic City, New Jersey, by the entire Board from Sunday, May 21, through Saturday, May 28, 1950. Formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates.

Candidates for re-examination in Part II must make written application to the Secretary's office not later than April 1, 1950.

Applications are now being received for the 1951 examinations. Application forms and Bulletins are sent upon request made to Paul Titus, M.D., Secretary, American Board of Obstetrics and Gynecology, Inc., 1015 Highland Building, Pittsburgh 6, Pennsylvania.

ACQUI RHEUMATOLOGY PRIZE COMPETITION

The Azienda Autonoma of the health resort of Acqui, Italy, has announced an international competition for an original and unpublished medical article on the physiopathology, clinical history and therapy of rheumatic and arthritic diseases. The competition is free and open to all Italian and foreign doctors. A prize of 1,000,000 Italian lire will be awarded by the international judging commission to the best article, or may be divided between two articles. Articles may be written in Italian, French, English, Spanish or German, and the work or works receiving the award will be published under the supervision of the Azienda Autonoma. The competition will close on December 31, 1950.

Further information and the rules of the competition may be obtained from the Azienda Autonoma di Cura Acqui, Piemonte, Italy.

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 3–MAY 19. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 286, issue of August 18.
JANUARY 9–DECEMBER 1. Laboratory Courses at Communicable Disease Center, Atlanta, Georgia. Page 950, issue of December 8.
MARCH 4–29. Springfield Hospital Educational Program. Page 347.
MARCH 6. New England Cardiovascular Society. Page 305, issue of February 23.
MARCH 7. Boston City Hospital House Officers' Association. Page 305, issue of February 23.
MARCH 8. New England Pediatric Society. Page 269, issue of February 16.
MARCH 8. Phi Lambda Kappa Lecture. Page 270, issue of February 16.
MARCH 8. Beth Israel Hospital Lecture. Page 270, issue of February 16.
MARCH 8. New England Society of Physical Medicine. Notice above.
MARCH 9. New England Diabetes Association. Notice above.
MARCH 9. Neck Tumors — Problems of Diagnosis and Management. Dr. Joseph Tartakoff. Pentucket Association of Physicians. 8:30 p.m. Haverhill.
MARCH 9-11. American Goiter Association. Page 234, issue of February 9.
MARCH 10. Public Seminar in Chemotherapy. Page 270, issue of February 16.
MARCH 14. New England Society of Anesthesiologists. Page 234, issue of February 9.
MARCH 14. Boston City Hospital House Officers' Association. Notice above.
MARCH 15. Beth Israel Hospital Lecture. Page 270, issue of February 16.
MARCH 17 AND 18 (note change of dates). New England Health Education Association. Page 305, issue of February 23.
MARCH 22. Beth Israel Hospital Lecture. Page 270, issue of February 16.
MARCH 23. Cornell Alumni Day. Page 234, issue of February 9.
MARCH 24. Public Seminar in Chemotherapy. Page 270, issue of February 16.
MARCH 29. Beth Israel Hospital Lecture. Page 270, issue of February 16.
APRIL 7. Public Seminar in Chemotherapy. Page 270, issue of February 16.
APRIL 17. Boston Lying-in Hospital Obstetric Round Table. Page 888, issue of December 1.
APRIL 22–29. American Association of Industrial Physicians and Surgeons. Page 305, issue of February 23.
APRIL 24–28. National Tuberculosis Association. Page 678, issue of October 27.

(Notices concluded on page xvii)

Dr. Wise has a curious notion
- - Inspired, perhaps, by a potion - -
If you liked his appearance,
Speed, tonnage and clearance,
You would write, to express that emotion.

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NOTICES (*Concluded from page 348*)

APRIL 26. New England Obstetrical and Gynecological Society. Rhode Island Hospital and Providence Lying-in Hospital, Providence, Rhode Island.

APRIL 29. Eastern Section of American Congress of Physical Medicine. Page 306, issue of February 23.

APRIL 29. Long Island College of Medicine Alumni Day. Page 348.

MAY 3. Norfolk District Medical Society Anniversary Dinner.

MAY 4. Suffolk District Censors' Meeting. Page 234, issue of February 9.

MAY 14–19. International and Fourth American Congress of Obstetrics and Gynecology. Page 160, issue of January 26.

MAY 16–18. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

MAY 17. Luncheon Meeting. Section on Diseases of the Eye, Ear, Nose and Throat, Massachusetts Medical Society. Hotel Statler, Boston. 12:00 m.

MAY 24–26. American Association of Genito-Urinary Surgeons. Page 234, issue of February 9.

JUNE 22–25. American College of Chest Physicians. Page 270, issue of February 16.

JUNE 24 AND 25. American Society for the Study of Sterility. Page 38, issue of January 5.

JULY 17–22. International Congress for Scientific Research. Page xvii, issue of September 1.

AUGUST 21–26. International Society of Hematology. Page 888, issue of December 1.

AUGUST 31–SEPTEMBER 7. World Federation for Mental Health. Page 306, issue of February 23.

SEPTEMBER 3–9. International Heart Congress. Page 160, issue of January 26.

SEPTEMBER 27–29. Mississippi Valley Medical Society. Page 991, issue of December 15.

NOVEMBER 1. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

DISTRICT MEDICAL SOCIETIES

NORFOLK

MARCH 28.
MAY 3. Anniversary Dinner.

SUFFOLK

MAY 4. Censors' Meeting.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, MARCH 9

FRIDAY, MARCH 10

*9:00 a.m.–12.00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.
12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.
*1:30 p.m. Tumor Clinic. Out-Patient Department, Mount Auburn Hospital, Cambridge.

MONDAY, MARCH 13

*11:30 a.m.–12:15 p.m. Chest X-Ray Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

TUESDAY, MARCH 14

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.
*7:00 p.m. Boston City Hospital House Officers' Association. Dowling Amphitheater, Boston City Hospital.

WEDNESDAY, MARCH 15

*11:00 a.m.–12:00 m. Medical Rounds. Children's Medical Center.
*12:00 m. X-Ray Conference. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.
*12:00 m.–1:00 p.m. Clinicopathological Conference (Children's Medical Center). Amphitheater, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Combined Clinic of all Medical Center Services. Amphitheater, Children's Hospital.
*7:30 p.m. Mechanism of Renal Water and Electrolytes. Dr. Charles H. Burnett. Beth Israel Hospital.

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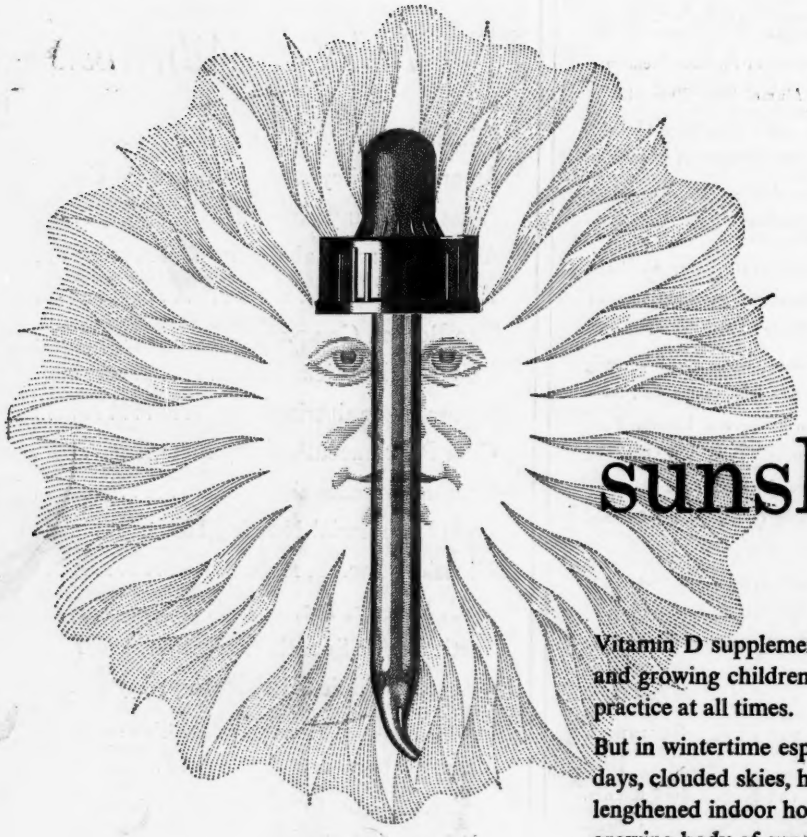

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